Oral appliance therapy in obstructive sleep Apnoea Syndrome

Doff, Michiel Hindrik Jan

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Long-Term Efficacy and Comorbidity

Michiel H.J. Doff

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Thesis

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t Hogelaand

Ede Staal (1941-1986)

Gronings

t Hogelaand
t Is de lucht achter Oethoezen,
t Is t torentje van Spiek,
t Is de weg van Lains noar Klooster,
En deur Westpolder langs de diek.

t Binnen de meulens en de moaren,
t Binnen de kerken en de börgen,
t Is t laand woar ik as kind
Nog niks begreep van pien of zörgen:
Dat is mien laand, mien Hogelaand...

t Is n doevetil, n dörpsstroat,
t Is n olle bakkerij,
t Binnen de grode boerenploatsen,
Van Waarvum, Oskerd, zo noar Mij.

t Is de waait, t is de hoaver,
t Is t koolzoad in de blui,
t Is de horizon bie Roanum,
Vlak noa n dunderbui:
Dat is mien laand, mien Hogelaand...

t Is n mooie oavend in maai,
n Kou houst doeknekt in t gruinlaand,
Ik heb veur d'eerste moal verkeren,
En vuil de vonken van dien haand.
De wilde plannen dij ik haar,
Komt sikkom niks meer van terecht,
Totdat de nacht van t Hogelaand,
n Donker klaid over ons legt:
Dat is mien laand, mien Hogelaand...

Nederlandse vertaling

Het Hogeland
Het is de lucht achter Uithuizen,
Het is het torentje van Spijk,
Het is de weg van Leens naar Kloosterburen,
En door Westpolder langs de dijk.

Het zijn de molens en de maren,
Het zijn de kerken en de borgen,
Het is het land waar ik als kind
Nog niets begreep van pijn en zorgen:
Dat is mijn land, mijn Hogeland...

Het is een duiventil, een dorpsstraat,
Het is een oude bakkerij,
Het zijn de grote boerenplaatsen,
Van Warffum, Usquert, zo naar Uithuizermeeden.

Het is de tarwe, het is de haver,
Het is het koolzaad in de bloei,
Het is de horizon bij Ranum,
Vlak na een donderbui:
Dat is mijn land, mijn Hogeland...

Het is een mooie avond in mei,
Een koe hoest voorover gebogen in het weiland,
Ik heb voor de eerste keer verkering,
En voel de vonken van jouw hand.
De wilde plannen die ik had,
Daar komt bijna niets meer van terecht,
Totdat de nacht van het Hogeland,
Een donker kleed over ons legt:
Dat is mijn land, mijn Hogeland...

Ter nagedachtenis aan mijn moeder

Contents

CHAPTER 1

Introduction and aims of the study

Obstructive Sleep Apnoea Syndrome

Sleep disorders commonly occur in the general population and may give rise to serious repercussions on general health, social life and daily functioning. The obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, which is characterized by intense snoring and recurrent obstructions of the upper airway during sleep (1, 2). These airway obstructions can either be complete (apnoeas) or partial (hypopnoeas) and can cause (possibly severe) oxygen desaturation of the blood. In order to restore airway patency, patients experience arousals from sleep as the sympathetic nervous system is activated (3). These arousals result in sleep fragmentation and therefore, restorative sleep stages are rarely reached. As a consequence of this deprived sleep, patients may suffer from excessive daytime sleepiness (EDS), impaired cognitive function and an increased risk of (traffic) accidents (4-6). Furthermore, the disorder is associated with various cardiovascular complications and an increased mortality when untreated (7).

The severity of OSAS is usually expressed as the apnoea-hypopnoea index (AHI), defined as the average number of apnoeas and hypopnoeas per hour sleep and is assessed through a sleep registration (e.g., polysomnography). During polysomnography, oronasal airflow, respiratory effort, oxyhemoglobin saturation, the level of snoring, sleeping position, limb movements, cardiac function (electrocardiography) and brain activity (electroencephalography) are registered. Based on the outcome of this polysomnographic study, OSAS is classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI> 30) (8).

During the mid-sixties of the 20th century it was discovered that sleepy obese individuals, suffered from obstructions of the upper airway during sleep and had repetitive awakenings during sleep (9). Since then the relationship between obesity and OSAS, particularly in midlife and old age, has been clearly established. Nowadays, the condition requires global attention and is the subject of intense scientific research. The disorder affects 4% of male and 2% of female adults in the North American population (10). Despite these rates it is estimated that 93% of the female and 82% of the male population with moderate to severe OSAS is still undiagnosed (11). In the Netherlands, the prevalence of clinically significant sleep apnoea syndrome in men, aged 35 years and older, is suggested to be at least 0.45% (12). Given the demographic shift in age and the predicted increase in body weight over the next years, the prevalence of OSAS is expected to rise furthermore.

Treatment of OSAS

When treating OSAS, clinicians may consider various non-invasive, surgical or pharmacological treatment modalities (13, 14). When conservative treatment is not applicable or effective, continuous positive airway pressure (CPAP) used to be the preferred intervention in OSAS patients. It appears that the primary mechanism for improvement in upper airway stabilisation by CPAP

administration is related to a mechanical splinting effect (15). Obstructions of the upper airway are avoided in this way or at least significantly reduced (16). Positive airway pressure is generated through a flow generator and is administered through an (oro)nasal mask. Although very effective, the obtrusive nature of the flow generator and (oro)nasal mask, may cause patients to cease or adhere poorly to CPAP therapy. (17, 18). Furthermore, CPAP therapy is associated with side-effects such as sneezing, nasal congestion and dryness of the airway mucosa. These side-effects have led to a search for simpler but effective treatment alternatives that match the effectiveness of CPAP.

Over the past decades, intra-orally worn dental devices, commonly known as oral appliances, have gained increasing popularity as treatment alternative to CPAP therapy. There are several types of oral appliances, including tongue-retaining devices, which hold the tongue in an advanced position. The most common type of oral appliance is the mandibular repositioning appliance (MRA). An MRA aims at relieving upper airway obstructions by positioning the mandible and its attached soft tissues structures in a forward and downward position during sleep (19).

Mandibular repositioning appliances can be divided into monoblock (one piece) and bi-block (two pieces) appliances. In monoblock appliances, the maxillary and mandibular acrylic components are joined together and do not allow for any mandibular movements. Furthermore, these appliances advance the mandible in a predefined ventral position. However, when a patient needs another maxillomandibular relationship to improve effectiveness of treatment or to improve comfort, a new MRA must be produced or the two parts must be separated and joined together again in the desired maxillomandibular relationship. In some situations this can be undesirable because the patient may have to sleep without the device for a short period. Bi-block appliances consist of two separate parts for both the maxilla and mandible with various mechanisms to join these parts together and to adjust the mandible in the desired ventral position (see figure 1, chapter 2). Final adjustment of the MRA is usually realized on the basis of subjective complaints (i.e. decreased EDS and reduction in snoring levels). However, a subjective improvement of symptoms does not always imply a normalization of the number of upper airway obstructions (i.e. AHI <5) and should therefore always be objectified by polysomnography.

Nowadays, oral appliance therapy has been demonstrated to be an effective alternative in treating OSAS, especially in the mild and moderate spectrum of the disorder and in patients unwilling or unable to tolerate CPAP therapy (20, 21). For patients with severe OSAS, CPAP therapy remains superior. There is however a lack of controlled studies comparing the efficacy of oral appliance therapy and CPAP therapy in the long term (≥ 2 years) in OSAS patients representing the entire spectrum of the disorder (e.g. mild-to-severe).

Wearing an oral appliance may be associated with side-effects. A distinction can be made between effects in the initial phase of treatment and side effects that occur after prolonged use

of an MRA. Symptoms in the early stages of therapy are usually related to the unnatural ventral position of the mandible during sleep. Side-effects that occur after long-term use of an oral appliance are mostly related to the patients' dentition.

Aims of this study

The general aims of this study were:

1. To study changes in upper airway morphology in patients wearing an oral appliance.
2. To reveal to what extent oral appliance- and CPAP therapy is effective in the long-term (2 years) in untreated patients, representing the entire spectrum of the disorder OSAS.
3. To evaluate side-effects of oral appliance therapy on the long-term.

Upper airway imaging provides insight into the complex pathophysiology of OSAS. There are several ways to image the upper airway in OSAS patients, including computed tomography (CT), magnetic resonance imaging (MRI) and videoendoscopy. Most of these imaging techniques are expensive, invasive or not readily available in clinical practice. Cephalometry is a widely available, less expensive, and easy to perform technique to examine upper airway craniofacial and soft tissue structures. It has also been used to visualize changes in upper airway morphology with an oral appliance in situ. However, to our knowledge, it is unclear whether there is a relationship between changes in the upper airway morphology with an oral appliance and the treatment response to oral appliance therapy.

In chapter 2, changes in upper airway morphology in OSAS-patients, wearing on oral appliance, will be assessed by means of cephalometric analysis.

Long-term efficacy of oral appliance therapy has already been described in a few studies. In some studies, respiratory parameters deteriorated in some patients during the follow-up period, even in patients who were treated successfully at the short-term. In some studies however, there was no (matched) control-group, no clear randomisation was described or only mild and moderate OSAS patients were included. Moreover, some studies included patients who had already been surgically treated for their OSAS.

Chapter 3 will focus on the long-term objective and subjective treatment response to oral-appliance- and CPAP therapy in untreated patients with mild-to-severe OSAS.

After starting oral appliance therapy, common side effects are pain in the temporomandibular joints (e.g. arthralgia) (22, 23), painful chewing musculature and their tendons (i.e. tendomyalgia) (24) and pain in the teeth (e.g. odontalgia) (19). Furthermore, hypersalivation (25) or symptoms of a dry oral mucosa (26) have been reported. Most of these symptoms can be characterized as mild and transient (22). In the long term, a decreased overjet and overbite (24, 25, 27, 28) have been described. Furthermore, the inclination of the upper and lower incisors can change (25) and a tendency to a mesial occlusion (27, 28) or a (bi)lateral open bite (29) has been reported.

In a recent study a distinction was made between negative and positive side effects (30). Positive side-effects include a correction of a class II into a class I occlusion or a decrease in overbite and overjet in class II occlusion. Negative side-effects are defined as shifts in occlusion, resulting in an end-to-end occlusion, a class III occlusion or a (bi)lateral open bite. When studying the literature regarding side effects as a result of long term oral appliance therapy, it can be concluded that most studies did not include a control group, small sample sizes were studied, only patients with mild or moderate OSAS were included or non-adjustable appliances were used. Therefore, it remains unclear to what extent side-effects occur, associated with long-term use of an adjustable oral appliance in patients representing the entire spectrum of the disorder. Furthermore, the possible association between the degree of mandibular protrusion and the extent of side-effects is not conclusive to date.

Chapter 4 will focus on possible side-effects of oral appliance therapy. Chapter 4.1 describes how we cephalometrically assessed possible side-effects on the craniofacial morphology associated with long-term use of a titratable oral appliance compared with CPAP. Secondly we studied the relationship between these possible side effects and the degree of mandibular protrusion during the follow-up period. In chapter 4.2 a controlled study is presented, in which dental side-effects of long-term oral appliance therapy are assessed on cast models. A controlled study on possible side-effects on the temporomandibular complex is finally described in chapter 4.3.

Maxillomandibular advancement (MMA) surgery has gained increasing popularity as a therapeutic alternative in OSAS patients as an extra-pharyngeal operation that enlarges and stabilizes the entire velo-oro-hypopharyngeal airway. This specific surgical procedure is indicated for treatment of severe OSAS in patients who cannot tolerate or who are unwilling to adhere to CPAP therapy, or in whom oral appliances, which are more often appropriate in mild and moderate OSAS patients, have been considered and found ineffective or undesirable (31).

In chapter 5 a case is described in which a female patient, with morbidly severe OSAS and mandibular retrognathia, was treated with an oral appliance. Although very effective, the patient was not satisfied with her facial profile and would also like a more permanent solution for her remaining severe OSAS. She therefore choose to undergo MMA surgery, combined with a chin osteotomy and submental liposuction.

Chapter 6 discusses the main findings of the studies described in this thesis (chapter 2 through 5) in a broader context and general conclusions are drawn.

Chapter 7 provides a summary of this thesis in English and Dutch.

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CHAPTER 2

Effects of an oral appliance on the upper airway morphology: a cephalometric analysis

This chapter is an edited version of:

Doff M.H.J., Hoekema A., Pruim G., van der Hoeven J., de Bont, L.G.M., Stegenga B. Effects of a Mandibular Advancement Device on the Upper Airway Morphology: a Cephalometric Analysis.

J Oral Rehabil 2009; 22: 390-398

Abstract

The aims of this study were to assess changes in the upper airway morphology associated with an oral appliance in situ in patients suffering from the obstructive sleep apnoea-hypopnoea syndrome and to relate these changes to treatment response.

Changes in upper airway morphology as a result of an oral appliance were assessed in 52 OSAS patients by means of cephalometric analysis. Lateral cephalograms were taken at baseline and after 2-3 months of treatment. Baseline and follow-up cephalograms were traced twice and cephalometric variables were compared. The predictive value of changes in upper airway morphology for the treatment response was evaluated in univariate and multivariate regression analyses.

Oral appliance therapy resulted in an increased posterior airway space at the level of the second vertebra, the uvular tip and the base of the tongue. The increase of the posterior airway space at the level of the second vertebra and the uvular tip were the best predictors for relative improvement of the apnoea-hypopnoea index. However, the predictive value for treatment response of these cephalometric upper airway changes should be interpreted with caution.

Introduction

The obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, characterized by repetitive partial (hypopnoea) or complete (apnoea) airway obstructions and disruptive snoring during sleep (1). These airway obstructions can cause recurrent arousals from sleep, ultimately resulting in excessive daytime sleepiness, neurocognitive impairment, a higher risk of motor-vehicle accidents and cardiovascular disease events (2-5).

Severity of the disorder is usually expressed by the apnoea-hypopnoea index (AHI), i.e., the mean number of apnoeas and hypopnoeas per hour sleep. OSAS may be classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30) (6). OSAS of at least mild severity is diagnosed in 2% of women and 4% of middle-aged men in the North-American population (7).

In order to improve upper airway patency during sleep, a variety of treatment options, ranging from non-invasive to surgical, is available. Continuous positive airway pressure (CPAP) is generally considered the treatment of first choice in severe OSAS cases (8). However, compliance with this relatively obtrusive therapy may be poor (9, 10). Oral appliance therapy is an effective alternative, and is especially effective in mild/moderate OSAS cases (2). Most oral appliances used in a clinical setting are mandibular advancement devices which keep the mandible and its attached musculature in a protruded position.

Upper airway imaging provides insight into the complex pathophysiology of OSAS. There are several ways of imaging the upper airway in OSAS-patients, including computed tomography (CT), magnetic resonance imaging (MRI) and videoendoscopy. Most of these imaging techniques are expensive, invasive or not readily available in clinical practice. Cephalometry is a widely available, less expensive, and easy to perform technique to examine upper airway craniofacial and soft tissue structures (11). It has also been used to visualize changes in upper airway morphology with an oral appliance in situ (12, 13). However, to our knowledge, it is unclear whether there is a relationship between changes in the upper airway morphology with an oral appliance and the treatment response to oral appliance therapy. To answer this question we determined changes in upper airway morphology in OSAS-patients by means of cephalometric analysis.

Materials & Methods

Patient selection

The effectiveness of an oral appliance in the treatment of OSAS, as compared to CPAP, has been determined in a separate randomized controlled trial (15). In that trial, patients with OSAS (apnoea-hypopnoea index > 5) (6) were recruited at the Department of Home Mechanical Ventilation of the University Medical Center Groningen, the Netherlands. Based on dental, medical and psychological criteria (Table 1), patients were selected for that trial and consequently randomized for either CPAP- or oral appliance therapy (15). In the course of that study, several patients switched from CPAP to oral appliance therapy.

For the present study, the patients who had been randomized to the oral appliance group (n=51)

Table 1. Criteria for exclusion.

Medical and psychological criteria	Dental criteria
Previous treatment of OSAS (continuous positive airway pressure [CPAP], oral appliance therapy, or uvulopalatopharyngoplasty)	Extensive periodontal disease or tooth decay
Morphological airway abnormalities requiring treatment	Active temporomandibular joint disease (including severe bruxism).
Endocrine dysfunction	Restrictions in mouth opening (<25 mm) or advancement of the mandible (<5 mm).
A reported or documented history of severe cardiac or pulmonary disease	Partial or complete edentulism (<8 teeth in upper or lower jaw).
Moderate or severe periodic limb movement disorder (periodic limb movement index >25)	
A psychological condition precluding informed consent (mental retardation or psychiatric disorder; e.g., depression or schizophrenia)	

as well as patients who had switched from CPAP to oral appliance therapy before follow-up (n=6) were included. Of the latter patients, five were considered non-compliant to CPAP and CPAP was nonsuccessful in one patient. Of the fifty-one patients, randomized to oral appliance-therapy, two were lost to follow-up. Furthermore, three patients were excluded because of an inadequate quality of the cephalograms, resulting in 52 patients for analysis. The present study was approved by the Groningen University Medical Center's Ethics Committee (METc2002/032). Written informed consent was obtained from patients before enrolment.

Study design

To determine whether there is a relationship between changes in upper airway morphology with an oral appliance in situ and treatment response to oral appliance therapy, patients had been subjected to a polysomnographic evaluation at baseline. In addition, a lateral cephalogram of all patients was taken. The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a protruded and downward position (Fig. 1). The mandibular protrusion could be adjusted with 0.2 mm increments with a propulsion screw, which was incorporated anteriorly in the oral appliance. Before starting oral appliance therapy, the maximal range of mandibular protrusion of each patient was determined with a George-Gauge™ (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at approximately 50% of the patient's maximal protrusion. After having adapted to this position during a two-week period, patients were allowed to further adjust the oral appliance during a 6 weeks period. After this "titration" period, the treatment effect was assessed with a second polysomnogram. This period was, if necessary, continued

Figure 1. Oral appliance in situ.

until the AHI was <5 or until the adjustments became uncomfortable for the patient. Follow-up review ended with a final polysomnographic evaluation or when the patient discontinued treatment (e.g., because of poor tolerance). Furthermore, a second lateral cephalogram was taken with the oral appliance intra-orally. The degree of protrusion and the vertical dimension of the oral appliance were kept constant during the follow-up measurements (e.g. second cephalogram and polysomnographic evaluation). Mandibular protrusion and the mouth opening (including the vertical overbite) were measured with a digital sliding calliper with a 0.01 mm accuracy.

The primary outcome measure was the change in upper airway morphology, associated with wearing an oral appliance. Secondary outcome measures were the relative improvement of the AHI, an AHI <5 and the criterion of "effectiveness of treatment" as suggested by Hoekema et al, (2) defined as an AHI <5 or a reduction in the AHI of at least 50% from the baseline value to a value of <20 in a patient without subjective OSAS symptoms (6) while using therapy (no excessive daytime sleepiness and <2 subjective OSAS symptoms) (appendix).

Polysomnography

Polysomnography (Embla® A10 digital recorder, Medcare, Reykjavik, Iceland) for baseline and follow-up evaluations was conducted ambulatory in the patient's home. Based on the AHI, patients were classified as having non-severe (AHI 5-30) or severe (AHI >30) OSAS. All polysomnograms were evaluated and scored by the same neurophysiologist (JH), who was unaware of the patient's treatment assignment.

Cephalometric analysis

All lateral cephalograms were recorded using a ProMax Cephalostat (Planmeca, Helsinki, Finland). The "mirror position" (16) was used in order to get a reproducible position of the head. Patients were instructed to swallow and to close their mouths with the mandible in maximal in-

Table 2. Demographic variables at baseline and follow-up.

Variable	Baseline * (n=52)	Follow-up* (n=52)	Significance of the difference
Age (years)	50.8 ± 9.5	-	-
Male / female ratio	45 / 7	-	-
Epworth sleepiness scale	12.8 ± 5.7	6.8 ± 5.4	$p < 0.05$
Apnoea-hypopnoea index (no/hour)	35.8 ± 27.5	7.3 ±13.6	$p < 0.05$†
OSAS severity	Non-severe: n=28 (54%) Severe: n=24 (46%)	-	-
Body-mass index (kg/m2)	31.8 ± 5.8	31.9 ± 5.9	NS
Neck circumference (cm)	43.6 ± 3.1	43.7 ± 3.0	NS
$minSaO_2$ (%)	79 ± 8	88 ± 7	$p < 0.05$

* Plus-minus values are means ± standard deviations.
Abbreviations: minSaO2 = lowest oxyhemoglobin saturation during sleep, NS = not significant.
† Statistical analysis after log transformation of the baseline and follow-up value.

tercuspation and the lips in a relaxed position. After a short period of relaxed tidal breathing the cephalogram was taken at end-expiration. A trace-protocol (Table 3, Fig. 2) was designed and all tracings were performed using Viewbox 3.1.1.6 software® (dHal software. Kifissia, Greece). As a first step, to determine inter-observer reliability, 10 baseline cephalograms were randomly chosen and traced by two experienced clinicians (GP, MD). Next, to minimize identification error, all 52 cephalograms were traced blindly with respect to treatment outcome by one observer (MD) and repeated after a one week period. Mean outcomes of both tracings were used for further statistical analysis. All linear cephalometric measurements were converted to values of life size.

Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (version 14.0, SPSS Inc., Chicago, IL, USA). To assess inter-observer reliability of the tracings, the interclass correlation coefficient (ICC) was calculated for each variable. ICCs < 0.4 were considered poor, ICCs of 0.4 to 0.75 were considered fair to good, and those > 0.75 were considered excellent (17).

All variables were normally distributed (AHI at baseline and follow-up after log transformation) and their means ± standard deviation are reported. To compare outcomes between demographic and cephalometric variables at baseline and follow-up, paired Student's *t*-tests were performed. α was set at 5%.

The differences in upper airway morphology between baseline and follow-up variables were selected for regression analysis. For matters of broad inclusion of possible determinants, was set at 0.2 for the univariate analyses. The dependent variable was the relative improvement of the

Table 3. Mean values of cephalometric variables at baseline and follow-up.

Variable	Baseline (n=52)		Follow-up with oral appliance (n=52)		95% CI of the difference	Significance paired t-test
	Mean	*SD*	*Mean*	*SD*		
Sagittal jaw relationship						
SNA (degrees)	80.3	4.6	80.1	4.5	[-0.1 0.7]	NS
SNB (degrees)	76.5	4.4	78.0	4.5	[-2.0 – -1.0]	p < 0 .05
ANB (degrees)	3.8	2.6	2.0	3.1	[1.2 – 2.3]	p < 0 .05
Pharyngeal dimensions						
C2a-P2a; perpendicular distance from point C2a to the anterior pharyngeal wall (mm)	13.1	3.3	14.5	3.9	[-2.3 – -0.5]	p < 0 .05
C2a-P2p; linear distance between point C2a and P2p (mm)	4.6	2.3	4.4	1.5	[-2.8 – 0.7]	NS
Pas-C2; posterior airway space at the level of the second vertebra; linear distance between P2a and P2p (mm)	8.5	3.5	10.1	3.7	[-2.6 – -0.6]	p < 0 .05
Pas-BT; linear distance between point BT and PPW' (mm)	8.7	3.4	9.9	3.3	[-2.2 – -0.1]	p < 0 .05
Pas-Ut; posterior airway space at the level of the tip of the velum; perpendicular distance from the tip of the velum to the posterior pharyngeal wall (mm)	7.5	2.6	9.4	3.1	[-2.6 – -1.1]	p < 0 .05
PNS-Ut; uvular length; linear distance between the posterior nasal spine and the tip of the velum (mm)	41.7	5.4	41.8	5.5	[-1.3 – 1.0]	NS
Hyoid bone position						
Hy-C3a; linear distance from hy to C3a (mm)	39.6	4.0	39.4	4.2	[0.6 – 1.0]	NS
Hy-MP; perpendicular distance from hy to the mandibular plane (mm)	28.6	5.2	19.5	5.5	[8.1 – 10.2]	p < 0 .05
Hy-SN; perpendicular distance from hy to line SN (mm)	121.0	8.2	117.6	7.9	[2.2 – 4.5]	p < 0 .05

Abbreviations: CI = Confidence interval, NS = not significant, SD = standard deviation.

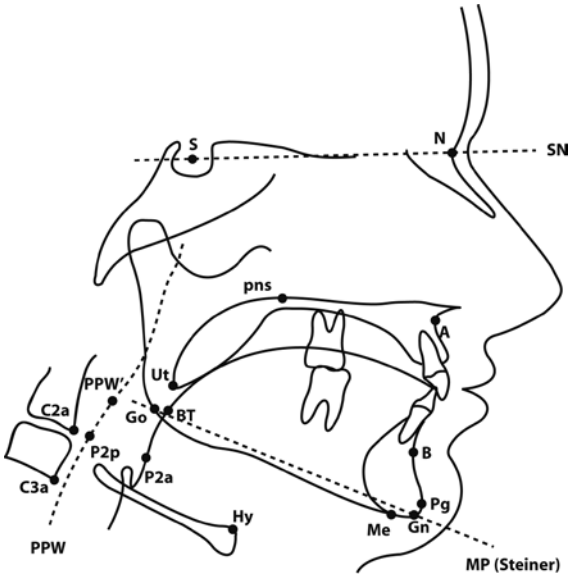

Figure 2. Cephalometric landmarks and reference lines traced on lateral cephalograms.
Seventeen reference points were identified on lateral cephalograms: A (point A) , B (point B), BT (Base of Tongue intersection; intersection point of the line connecting B-Go with the Base of Tongue), C2a (most antero-inferior point on the second vertebra), C3a (most antero-inferior point on the third vertebra), Gn (gnathion), Go (gonion), Hy (hyoid: the most antero-superior point on the body of the hyoid bone), Me (menton), N (nasion), Pg (pogonion), pns (posterior nasal spine), P2a (point created by the intersection of a perpendicular line from C2a with the anterior pharyngeal wall), P2p (point created by the intersection of a perpendicular line through C2a with the anterior pharyngeal wall, located on the posterior pharyngeal wall), PPW' (Posterior Pharyngeal Wall intersection; intersection point of the line connecting B-Go with the Posterior Pharyngeal Wall), S (sella), Ut (uvular tip; tip of the velum).
Three reference lines where identified on lateral cephalograms: MP (mandibular plane according to Steiner: the line through gonion and gnathion), PPW (posterior pharyngeal wall: the anterior outline of the posterior pharyngeal wall), SN (sella-nasion line).

apnoea-hypopnoea index following treatment for the linear regression analysis, and the presence or absence of "effectiveness of treatment" and an AHI < 5 following treatment for the logistic regression analysis. All significant variables concerning pharyngeal dimensions resulting from univariate linear and logistic regression analyses were then submitted for multivariate linear regression analysis.

Results

Treatment response

Demographic variables of all patients and variables regarding treatment response at baseline and follow-up are summarized in table 2. According to Hoekema's definition of success, treatment was "successful" in 42 patients (81%). The average mandibular protrusion for patients with effective treatment according to Hoekema (successful) at the follow-up review was 79.9 ± 18.1 % (mean ± s.d.) and 76.2 ± 18.1 % for the patients in which treatment was not effective (non successful). The difference in mandibular protrusion between the successful and nonsuccessful responder was not significant (*t*-test, $p > 0.05$). The average mouth opening at follow-up, when

Table 4. Interobserver reliability for tracings from random baseline cephalograms (n=10).

Variable	ICC	95% CI
Sagittal jaw relationship		
SNA	0.97	[0.69 – 0.99]
SNB	0.86	[0.31 – 0.97]
ANB	0.91	0.69 – 0.98]
Pharyngeal dimensions		
C2a-P2a	0.96	[0.30 – 0.99]
C2a-P2p	0.83	[0.49 – 0.96]
Pas-BT	0.69	[0.18 – 0.91]
Pas-C2	0.95	[0.78 – 0.99]
Pas-Ut	0.90	[0.6 – 0.97]
PSN-Ut	0.94	[0.78 – 0.99]
Hyoid bone position		
Hy-C3a	0.93	[0.22 – 0.99]
Hy-MP	0.92	[0.70 – 0.98]
Hy-SNL	0.95	[0.81 – 0.99]

See legend fig.2
Other abbreviations: CI = confidence interval, ICC = interclass correlation coefficient.

the patient was wearing the oral appliance, was 13.2 ± 2.8 mm in the successful responder group and 12.2 ± 2.4 mm in the nonsuccessful responder group. The latter difference between these two groups was not significant (*t*-test, $p > 0.05$).

Reliability

An "excellent" agreement between both examiners was found for all cephalometric variables (Table 4), except for the posterior airway space at the level of the base of the tongue (Pas-BT) which demonstrated "fair to good" agreement (17).

Cephalometric analysis

Regarding the sagittal jaw relationship the SNB-angle increased 1.5 (± 1.9) degrees and the ANB-angle decreased 1.8 (± 2.0) degrees as a result of wearing an oral appliance (Table 3). Concerning pharyngeal dimensions, increases were found for the posterior airway space at the level of the base of the tongue (Pas-BT) (1.2 ± 3.6 mm), at the level of the second vertebra (Pas-C2) (1.6 ± 3.7 mm), and at the level of the uvular tip (Pas-Ut) (1.8 ± 2.6 mm) with the oral appliance intra-orally. Moreover, both the distance from the hyoid to the mandibular plane (Hy-MP) and the distance between hyoid and the sella-nasion line (Hy-SN) had decreased (-9.2 ± 3.8 mm and -3.4 ± 4.1 mm, respectively), indicating a more cranial position of the hyoid bone.

Table 5. Univariate analysis of cephalometricvariables predicting a relative improvement of the apnoea-hypopnoea index with oral appliance therapy and logistic regression analysis for predicting an AHI<5 or 'effectiveness of treatment'‡ with oral appliance therapy.

Variable	↓AHI%† (Beta)	95% CI	AHI<5 (OR)	95% CI	Effectiveness of treatment‡ (OR)	95% CI
Sagittal jaw relationship						
SNB (degrees)	-0.07	[-5.60 – 5.47]	1.36	[1.0 – 1.86]	0.98	[0.68 – 1.41]
ANB (degrees)	0.74	[-4.70 – 6.18]	0.76	[0.55 – 1.03]	1.08	[0.75 – 1.55]
Pharyngeal dimen						
C2a-P2a (mm)	-0.23	[-3.57 – 3.12]	0.93	[0.78 – 1.11]	1.00	[0.80 – 1.24]
Pas-C2 (mm)	-3.37	[-6.11 – -0.63]*	0.85	[0.70 – 1.02]	0.91	[0.77 – 1.07]
Pas-BT (mm)	-2.70	[-5.53 – 0.13]	0.89	[0.75 – 1.06]	0.90	[0.76 – 1.07]
Pas-Ut (mm)	-5.36	[-9.16 – -1.56]*	0.99	[0.80 – 1.23]	0.77	[0.58 – 1.01]
Hyoid bone position						
Hy-MP (mm)	-0.54	[-3.34 – 2.27]	0.94	[0.81 – 1.10]	0.95	[0.78 – 1.14]
Hy-SN (mm)	-0.86	[-3.45 – 1.74]	0.92	[0.79 – 1.07]	0.97	[0.80 – 1.16]

* $p<0.05$.
† Relative decrease of the apnoea-hypopnoea index as a result of oral appliance therapy.
‡ Treatment was considered effective when the AHI either was <5 or showed substantial reduction, defined as reduction in the AHI of at least 50% from the baseline value to a value of <20 in a patient without symptoms while using therapy.
Abbreviations: AHI = apnoea-hypopnoea index, CI = Confidence interval, OR = Odds Ratio.

Regression analyses

Univariate linear regression analysis demonstrated that an increased posterior airway space at the level of the second vertebra (Pas-C2) and at the level of the uvular tip (Pas-Ut) was significantly associated with a relative improvement of the AHI (Table 5). Logistic regression analysis for predicting an AHI <5 or "effectiveness of treatment" did not yield any significant predictive cephalometric variables.

Multivariate linear regression analysis for predicting the extent of the relative improvement of the AHI, yielded a model with the increase in posterior airway space at the level of the uvular tip (Pas-Ut) as strongest predictor (beta = -5.40, 95% CI [-9.16;-1.56], $p<0.05$).

Discussion

The results of this study show that an oral appliance in situ improves the antero-posterior dimensions of the posterior airway space at the level of the second vertebra (Pas-C2), the uvular tip (Pas-Ut), and the base of the tongue (Pas-BT). At the former two sites the increased posterior airway space was associated with a relative improvement of the AHI.

No significant changes could be demonstrated in the linear distance between point C2a and P2p, suggesting that the increase of the posterior airway space at the level of C2 is caused by a more ventral position of the anterior pharyngeal wall. The increase in the posterior airway space can be attributed to the oral appliance, which holds the mandible in an anterior position. Isono et al (18) proposed possible mechanical interactions in the pharyngeal region. Since the tongue is directly connected to the mandible, a more anterior position of the mandible most likely displaces the tongue anteriorly, thus increasing the retroglossal airway space. Considering the working mechanism of an oral appliance (i.e. protruding the mandible and its attached soft tissue structures) one would expect the largest increase in posterior airway space to be located at the level of the base of the tongue. However, we found the largest increase at the level of the uvular tip. The first explanation for this finding is that in most OSAS patients the base of the tongue opposes the anterior wall of the soft palate because of macroglossia and/or a longer uvula associated with the disorder (19). By forcing the tongue in a more anterior position, the gravitational effect on the soft palate may be decreased. The resulting increase of the velopharyngeal airway space (Pas-Ut) with oral appliance therapy might be explained by this theory. A second explanation may be the decrease in snoring levels accompanied with oral appliance therapy, which might result in a decrease in oedematous tissue of the velum. Both explanations seem viable but it is unknown to what extent each of both mechanisms contributes to this increase in velopharyngeal airway space.

In several studies a more inferiorly positioned hyoid bone has been described in OSAS patients when compared to healthy subjects (14, 20, 21). In this study we demonstrated a more cranial position of the hyoid bone as a result of an oral appliance, as indicated by a decrease in the linear distance between hyoid and the sella-nasion line (Hy-SN) and the linear distance between hyoid and the mandibular plane (Hy-MP). Although the decrease in Hy-SN indicates a more cranial position of the hyoid bone, the decrease in distance between hyoid and the mandibular plane Hy-MP most likely results from the mouth opening associated with wearing an oral appliance. The more cranial position of the hyoid bone might also be the result of the more protruded position of the mandible and tongue with the oral appliance intra-orally. Consequently, the tongue musculature might pull the hyoid bone to a more anterior-superior position. However, contrary to other results, (22) we could not demonstrate a more anterior position of the hyoid bone with an oral appliance as indicated by a non-significant change in the linear distance between point hyoid (Hy) and the most antero-inferior point on the third vertebra (C3a). This difference in hyoid position could be explained by the fact that Tsuiki et al (23) recorded their cephalograms in the supine position. The gravitational effect on the antero-posterior position of the hyoid bone is probably

larger in supine position than in the upright position. This gravitational effect could have resulted in a more posteriorly located hyoid bone at baseline and consequently in a more anterior position with an oral appliance.

In this study, cephalograms were taken in an upright rather than a supine position. Ingman et al (24) reported that OSAS patients are prone to significant narrowing of their oropharyngeal airway, but not of their naso- or hypopharyngeal airway in the supine position. The findings in our patients may not be completely representative of the "normal" situation during sleep. However, in selecting suitable patients for oral appliance therapy in a clinical setting, the added value of supine cephalometry should be questioned because of its more laborious nature.

Sophisticated techniques like sleep nasendoscopy and a remotely controlled mandibular positioner have been suggested to predict the response to oral appliance therapy (25, 26). These techniques may be of additional value in selecting suitable candidates for oral appliance therapy. However, unlike cephalometry, most of these techniques are expensive and complex or not available in a dental or orthodontic practice. Cephalometry provides two-dimensional information. Imaging techniques providing three-dimensional information could be of additional value in assessing the complex pathophysiology of OSAS and the working mechanism of an oral appliance during sleep. On the other hand, these imaging techniques would be impractical and expensive in large groups of patients. Therefore, the present study aimed at providing predictive upper airway variables convenient for the clinical situation.

Multivariate linear regression analyses yielded a single-variate predictive model, with a positive change in posterior airway space at the level of the uvular tip (Pas-Ut) being the best predictor for a relative improvement of the AHI. However, logistic regression analysis for predicting an AHI <5 or "effective treatment" did not yield any predictive variables. Therefore, it could be hypothesized that the actual positive changes in upper airway dimensions with an oral appliance during sleep are not the main contributors to treatment response. In Table 3 it is shown that these actual changes are rather small (i.e. 0.1-2.2 mm). Therefore, it seems a plausible explanation that the effectiveness of an oral appliance is largely based on protecting the posterior airway space from collapsing during sleep rather than on increasing it. Another possible explanation is that obstructive sleep apnoea patients experience a greater degree of lateral than antero-posterior increase in airway size with an oral appliance (27). Therefore we conclude that, considering these possible mechanisms and some methodological limitations of this study (i.e. awake, upright position, two-dimensional), the predictive value for treatment response of these cephalometric upper airway changes should be interpreted with caution.

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CHAPTER 3

Oral appliance versus CPAP in obstructive sleep apnoea syndrome; a two-year follow-up

Submitted

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Oral Appliance versus CPAP in Obstructive Sleep Apnoea Syndrome; a Two-Year Follow-Up.

Abstract

In this study we report about the subjective and objective treatment outcome of oral appliance therapy and continuous positive airway pressure (CPAP) in a two-year follow-up of a cohort of 103 patients of a previously conducted randomized controlled trial.

Objective and subjective parameters were assessed after one year and two years of treatment. Treatment was considered "successful" when the apnoea-hypopnoea index (AHI) was <5 or showed 'substantial reduction', defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient without OSAS-symptoms while using therapy.

Regarding the proportions of successful treatments, no significant difference was found between oral appliance therapy and CPAP in treating mild-to-severe OSAS in a two-year follow-up. CPAP was still successful in 67.3% of the patients and oral appliance therapy in 52.9% of the patients ($p=0.14$) after two years of treatment. More patients dropped out under oral appliance therapy (47%) compared to CPAP (33%). Both therapies showed substantial improvements in polysomnographic and neurobehavioral outcomes. However, CPAP was more effective in lowering the AHI and showed higher oxygen saturation levels compared to oral appliance therapy ($p<0.05$).

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, characterized by snoring and repetitive pharyngeal collapse (1). It is associated with excessive daytime sleepiness, a decreased quality of life, increased cardiovascular morbidity, and a higher risk of traffic accidents (2, 3). The standard treatment, i.e. continuous positive airway pressure (CPAP), reduces upper airway obstructions and improves quality of life (4). However, because of its cumbersome nature, patients may have problems to adhere to or even abandon the treatment. Oral appliance therapy has been shown to be non-inferior to CPAP regarding treatment-success in mild-to-moderate OSAS patients in the short-term (5). Furthermore, many patients prefer oral appliance therapy to CPAP (6).

Long-term outcomes of oral appliance therapy have already been described in a few studies (7-11). In four studies, respiratory parameters deteriorated in some patients during the follow-up period, even in patients who were treated successfully at the short-term follow-up (7, 8, 10, 11). Some studies have been restricted to only mild and moderate OSAS-patients or included patients who had already been surgically treated for their OSAS. To our knowledge, no published parallel study has evaluated the two-year outcome of oral appliance- versus CPAP therapy in previously untreated patients with mild-to-severe OSAS.

The primary aim of this parallel cohort study was to evaluate the two-year objective and subjective outcome of oral appliance- and CPAP therapyin OSAS patients, representing the entire spectrum of the disorder and to gain more insight in the specific indications for both treatments. In this study we report about the two-year follow up of a cohort of a previously conducted randomized controlled trial (RCT) (5).

Materials & Methods

Patients and study protocol

After assessing 228 OSAS patients, 103 participants were finally recruited (between September 2002 and August 2005) for the previously conducted and reported RCT (ISRCTN18174167) (5) at the Department of Home Mechanical Ventilation of the University Medical Center Groningen, The Netherlands. Individuals over 20 years old who underwent polysomnography were eligible and were selected based on predefined medical, dental and psychological criteria (appendix). This study was approved by the Groningen University Medical Center's ethics committee (METc2002/032). Written informed consent was obtained from all patients before enrolment. Block randomization was used to allocate participants to either oral appliance therapy or CPAP therapy (12). It was not possible to blind patients or clinicians to treatment assignment. At baseline, each participant underwent a physical examination (appendix). Severity of disease was assessed based on the apnoea-hypopnoea index (AHI), i.e. the mean number of apnoeas and hypopnoeas per hour of sleep. Participants were classified as having non-severe (AHI 5-30) or severe (AHI ≥ 30) OSAS. More detailed information is provided in the appendix.

Study Design

For this follow-up study, polysomnographic and subjective evaluations were carried out after one year (T15) and two years (T27) of treatment. Treatment was considered *successful* when the AHI was <5 or showed a substantial reduction, defined as a reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient without subjective OSAS-symptoms while using therapy (no excessive daytime sleepiness and <2 subjective OSAS symptoms) (appendix). Participants not meeting these criteria at any follow-up review were considered *nonsuccessful*. Patients for whom oral appliance- or CPAP therapy was successful continued the treatment. If either treatment was not successful at any time during the follow-up period, patients were offered the alternative therapy (CPAP or oral appliance, respectively), which was thereupon titrated in the same fashion as the initial therapy. Patients who discontinued treatment for any reason were considered *nonadherent* to treatment (worst-case scenario). More detailed information on the results of the two-month follow-up (T2) has been published previously (5).

Interventions

The oral appliance (Thornton Adjustable Positioner type-1, Airway Management, Inc., Dallas, TX, USA) positioned the patient's mandible in a forward and downward position. This type of oral appliance is also known as a mandibular advancement device. By turning a propulsion screw, which was incorporated anteriorly into the appliance, patients could adjust the mandibular advancement in 0.2 mm increments. When initiating oral appliance therapy (T0), the mandible was set at 50% of the patient's maximal protrusion. After having adapted to this position during a two-week period, patients were allowed to further adjust the oral appliance during a six-week period. They were instructed to advance the mandible until symptoms abated or until further advancement caused discomfort. Subsequently, the treatment effect was assessed with a polysomnographic evaluation (T2). If necessary, the adjustment period was extended until the AHI was <5 or until the adjustments became uncomfortable for the patient. The titration period ended with a final polysomnographic evaluation or when the patient discontinued treatment (e.g., because of poor tolerance).

CPAP titration, aimed at abolishing all signs of apnoeas, hypopnoeas and snoring was performed during an afternoon nap (13).

Polysomnography

Polysomnographic studies (Embla® A10 digital recorder, Medcare, Reykjavik, Iceland) for baseline and all follow-up reviews were conducted while participants slept at home and were evaluated according to standardized criteria (appendix). All polysomnographic evaluations were evaluated and scored by the same neurophysiologist (JH), who was unaware of the patient's treatment assignment.

Physical and neurobehavioral examinations

Physical examination at baseline and follow-up reviews included documentation of height,

weight, neck circumference, alcohol consumption, tobacco use, and current medications. For the neurobehavioral examinations, patients completed the following questionnaires at all time-points: the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ) addressing OSAS-related symptoms (14, 15), and the 36-item short-form health survey (SF-36) evaluating health perceptions (16) (appendix). Furthermore, compliance rates were scored at all time points using a questionnaire.

Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). All continuous baseline variables were normally distributed and their means with standard deviations (s.d.) are reported. The AHI in the oral appliance- and CPAP group at baseline was normally distributed after logarithmic transformation. Medians and interquartile ranges are reported for variables with a skewed distribution. Details about the sample size calculation regarding the previously conducted two-month RCT have previously been described (5) and is also described in the appendix.

The primary outcome measure of this follow-up study was the difference in proportions of successful treatments between oral appliance- and CPAP therapy at different time-points.

Secondary outcome measures were polysomnographic and neurobehavioral outcomes at different time-points. To compare polysomnographic and neurobehavioral outcomes at different time-points, Student's t-tests were performed for outcomes with a normal distribution and Mann-Whitney U tests for outcomes with skewed distributions. Although proper randomization is executed, a (small) difference in the average values of a determinant for the two treatment arms may occur. To statistically correct this regression-to-the-mean phenomenon in our analysis when comparing T27 values with baseline values, the baseline value was at all times included in the regression model (i.e. auto-regression analysis model).

Comparison of the proportions of successful treatments between both treatments (Chi-square test) was also performed as function of disease severity (pre-specified subgroup analysis). The difference in dropout rates between both treatments was analyzed, using Chi-square test. The significance level of all analyses was set at 5%.

Results

One hundred and three patients were enrolled into the RCT. Randomization resulted in an oral appliance group of 51 patients and a CPAP group of 52 patients (Table 1). A flow diagram, summarizing the distribution of the patients is shown in figure 1. In the oral appliance group, 27 patients (53%) completed the two-year follow-up successfully still using their oral appliance (figure 1; group A). Seven more patients of this group completed the follow-up after switching to CPAP therapy (figure 1; group C), because they were considered nonsuccessful to oral appliance therapy (Table 1, appendix). In the CPAP group 35 patients (67%) completed the two-year follow-up successfully still using their CPAP (figure 1; group D). Another four patients switched to oral

Table 1. Characteristics of randomized patients.

Variable	Oral appliance* (n = 51)	CPAP* (n = 52)
Male/female ratio	43/8	49/3
Non-severe sleep apnoea (no. patients)	25	25
Severe sleep apnoea (no. patients)	26	27
Apnoea-hypopnoea index (no/hour)	39 ± 31	40 ± 28
Age (years)	49 ± 10	49 ± 10
Body-mass index (kg/m2)	32 ± 6	33 ± 6
Neck circumference (cm)	44 ± 4	45 ± 4

* Plus-minus values are means ± standard deviations.
Abbreviations: CPAP = continuous positive airway pressure.

appliance therapy during the follow-up period (3 were considered nonadherent to CPAP therapy, and 1 patient nonsuccessful). Of these 4 patients, 2 completed the two-year follow-up (figure 1; group B). The 7 patients (group C) who had switched to CPAP after oral appliance therapy had a higher baseline AHI (p=0.17), Body Mass Index (BMI) (p=0.02) and age (p=0.28) than the 4 patients (group B) who had switched from CPAP to oral appliance therapy (table E1, appendix).

In the oral appliance group 1 patient switched to CPAP after the two-month follow-up because of his profession as a truck driver, although treatment with an oral appliance was considered successful (AHI dropped from 69 to 17). Though, from a judicial point of view, an AHI of 17 is still considered as moderate OSAS and is not allowed in his profession in the Netherlands. From that point he refused further participation in this study. In the CPAP group, 1 patient dropped out because of adherence problems after the two-month follow-up although treatment was effective. He was treated with an oral appliance from that point but refused further participation in this study. Demographic variables of the patients that completed the two-year follow-up are provided in table 2 of the appendix.

Notwithstanding the fact that weight loss was always encouraged, the BMI did not significantly change in both treatment groups during the follow-up period.

The follow-up period (including the RCT period) started in October 2002 and ended in October 2007. The mean follow-up for the oral group was 2.3 ± 0.2 years (mean ± s.d.) and 2.4 ± 0.3 years for the CPAP group. This difference was not significant.

Subjective compliance rates did not significantly differ between both treatments. CPAP and oral appliance mean use was 6.8 ± 0.8 and 6.7 ± 0.7 nights per week respectively. Furthermore CPAP- and oral appliance therapy was used 6.9 ± 1.2 and 7.2 ± 0.8 hours per night.

More patients (not significant) dropped out under oral appliance therapy (47%) compared to CPAP (33%).

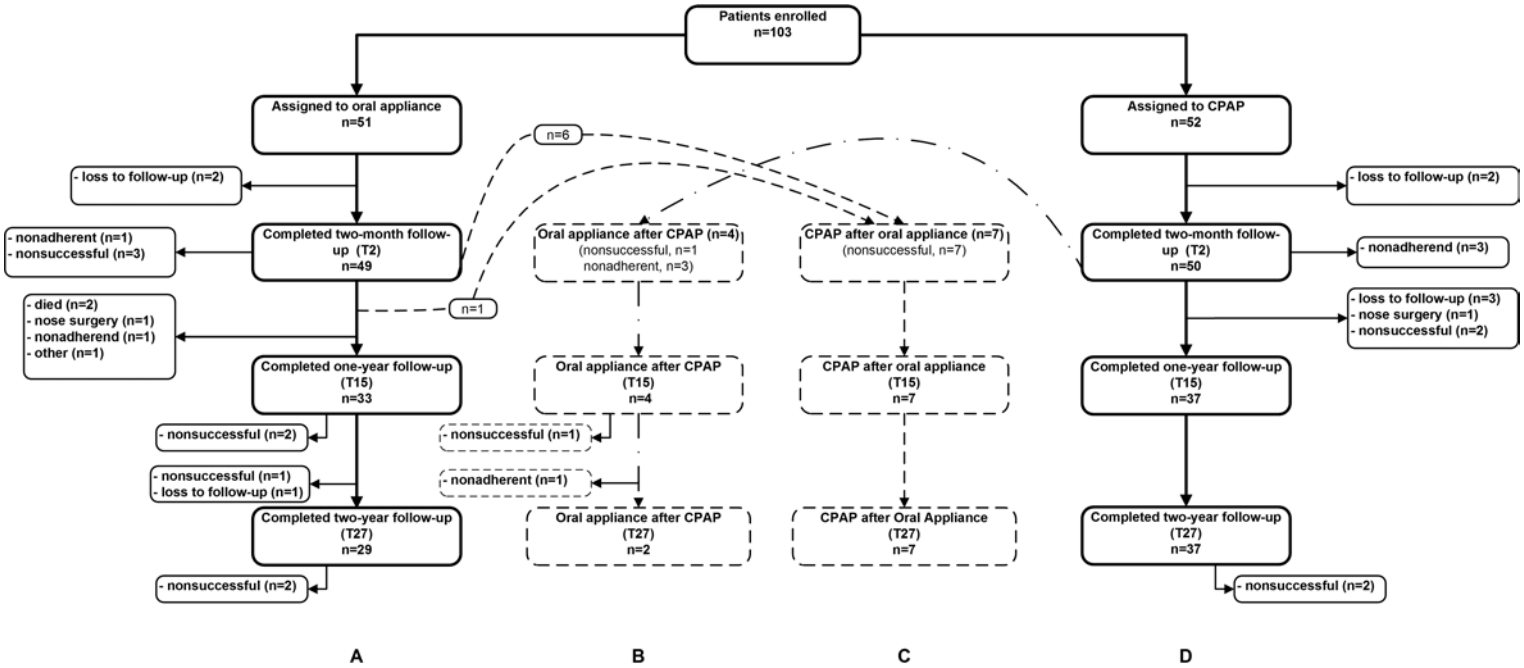

Figure 1. Flow diagram of participants throughout each phase of the follow-up period.

Table 2. Proportions of successful treatments with an oral appliance or with continuous positive airway pressure at different time points.

Successful treatment‡	Two-month follow-up (T2)*†‡		One-year follow-up (T15)*†‡		Two-year follow-up (T27)*†‡	
	Oral appliance	CPAP	Oral appliance	CPAP	Oral appliance	CPAP
Total population	39 / 51 (76.5%)	43 / 52 (82.7%)	31 / 51 (61.0%)	37 / 52 (71.2%)	27/ 51 (52.9%)	35 / 52 (67.3%)
Non-severe sleep apnoea	21 / 25 (84.0%)	20 / 25 (80.0%)	16 / 25 (64.0%)	16 / 25 (64.0%)	14 / 25 (56.0%)	15 / 25 (60.0%)
Severe sleep apnoea	18 / 26 (69.2%)	23 / 27 (85.2%)	15 / 26 (57.7%)	21 / 27 (77.8%)	13 / 26 (50.0%)	20 / 27 (74.1%)

*Values are the number of successful treatments divided by the total number of patients. Values in parenthesis are the percentages of successful treatments.
†Treatment was considered successful when the apnoea-hypopnoea index (***i.e.***, mean number of apnoeas and hypopnoeas per hour of sleep) either was <5 or showed "substantial reduction," defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no symptoms while using therapy.
‡ No significant differences (chi-square test) were found in the proportions of successful treatments between oral appliance- and CPAP therapy.
Abbreviations: CPAP = continuous positive airway pressure.

Table 3. Polysomnographic outcomes at different time-points of all patients who completed the entire follow-up period with the treatment that was assigned at baseline.

Variable	Baseline*		Two-month follow-up (T2)*		One-year follow-up (T15)*		Two-year follow-up (T27)*	
	Oral appliance (n =51)	CPAP (n = 52)	Oral appliance (n = 47)	CPAP (n = 47)	Oral appliance (n =33)	CPAP (n = 37)	Oral a ppliance (n =29)	CPAP (n = 37)
Apnoea-hypopoea index‡	39 ± 31	40 ± 28	2 (0-10) [0-73]	0 (0-3) [0-20]	2 (0-5) [0-15]	0(0-1)¶ [0-13]	2 (1-8)†† [0-42]	0 (0-1)¶†† [0-27]
Lowest oxyhemoglobin saturation (%)	78 ± 9	78 ± 10	88 ± 6	90 ± 6	88 ± 5	91 ± 4**	88 ± 5††	91 ± 4**††
Sleep efficiency (%)†	88 ± 10	86 ± 16	86 ± 8	86 ± 10	88 ± 7	89 ± 8	89 ± 8††	86 ± 10
Total sleep time (min.)	408 ± 70	390 ± 80	425 ± 64	405 ± 68	433 ± 63	433 ± 60	440 ± 62††	431 ± 70
Non-REM sleep stage 1 & 2 (%)‖	65 ± 13	68 ± 15	53 ± 10	54 ± 10	53 ± 7	53 ± 10	52 ± 9††	55 ± 10††
Non-REM sleep stage 3 & 4 (%)‖	14 ± 9	13 ± 12	20 ± 8	22 ± 8	20 ± 7	23 ± 9	21 ± 7††	22 ± 9††
REM sleep (%)‖	21 ± 8	19 ± 7	27 ± 7	24 ± 6	26 ± 6	25 ± 6	27 ± 6††	24 ± 6††

* Plus-minus values are means ± standard deviations; values with additives in parenthesis are medians with interquartile ranges. In square brackets ranges are provided.
† Sleep efficiency is the total sleep time expressed as a percentage of the total time in bed.
‡ The apnoea-hypopnoea index is the mean number of apnoeas and hypopnoeas per hour of sleep.
‖ Sleep stages are expressed as a percentage of total sleep time.
¶ Significant difference ($p<0.05$) between CPAP and oral appliance therapy (Mann-Whitney U test).
** Significant difference ($p<0.05$) between CPAP and oral appliance therapy (unpaired Student's t-test).
†† Significant difference ($p<0.05$) between baseline and the and two-year follow-up values (paired Student's t-test).
Abbreviations: CPAP = continuous positive airway pressure, REM = rapid eye movement.

Treatment outcome

Table 2 shows the proportions of successful treatments at the different time-points. After two years, treatment of the 51 patients randomized to the oral appliance group was successful for 27 (52.9%) patients ((14 out of 25 patients with non-severe OSAS (56.0%) and 13 of the 26 severe OSAS patients (50.0 %)). Of the 52 patients intentionally treated with CPAP, 35 (67.3%) were successfully treated (15 out of 25 patients with non-severe OSAS (60.0%), and 20 out of 27 patients (74.1%) with severe OSAS). The differences in proportions of successful treatments between both treatments were not significant. Proportions of successful treatments after applying the criterion AHI<5, are provided in table 3 of the appendix.

Polysomnographic outcomes

The AHI was significantly lower in the CPAP group after one year (0.0 (0.0-13.0)) (median with range) compared to oral appliance therapy (2.0 (0.0-15.0)), and after two years of treatment with CPAP (0.0 (0.0-27.0) versus oral appliance therapy (2.0 (0.0-42.0)) (table 3). This significant difference in advantage of CPAP therapy was also found for the lowest oxyhemoglobin saturation at the one- and two-year follow-up (at both time points 91 ± 4% with CPAP versus 88 ± 5% with oral appliance therapy).

Neurobehavioral outcomes

Both treatments yielded comparable improvements in the Epworth sleepiness score, the FOSQ-score and scores of the SF-36 at all time-points (table 4). Most of the variables improved significantly compared to the baseline values. No significant differences were found between both treatments.

Side-effects

Mild and 'transient' side-effects were commonly reported in the initial period of oral appliance therapy and include tooth pain, temporomandibular joint pain, myofascial pain, dry mouth and excessive salivation. Furthermore, we found that long-term oral appliance therapy and CPAP may result in dental changes in OSAS patients. Concerning this cohort, more detailed information regarding side-effects, associated with long-term oral appliance therapy and CPAP is provided in chapter 4.1-4.3 (17-19).

Table 4. Neurobehavioral outcomes at different time-points of all patients who completed the two-year follow-up period with the treatment that was assigned at baseline.

Variable‡	Range	Baseline*		Two-month follow-up (T2)*		One-year follow-up (T 15)*		Two-year follow-up (T27)*	
		Oral appliance (n =51)	CPAP (n = 52)	Oral appliance (n =49)	CPAP (n = 50)	Oral appliance (n =33)	CPAP (n = 37)	Oral appliance (n =29)	CPAP (n = 37)
Epworth sleepiness scale(↓)	*0-24*	*13 ± 6*	*14 ± 6*	*7 (2–10)*	*6 (4–12.0)*	*5 (3-8)*	*5 (2-9)*	*4 (1-8)‖*	*5 (1-8)‖*
Functional outcomes of sleep questionnaire									
- general productivity (↑)	1-4	3.0 ± 0.7	3.0 ± 0.8	3.5 ± 0.6	3.5 ± 0.7	3.5 ± 0.7	3.6 ± 0.7	3.6 ± 0.7¶	3.6 ± 0.6¶
- social outcome (↑)	1-4	2.9 ± 0.9	3.0 ± 1.0	3. 6± 0.7	3.6 ± 0.7	3.4 ± 0.9	3.7 ± 0.7	3.6 ± 0.9¶	3.8 ± 0.5¶
- activity level (↑)	1-4	2.6 ± 0.8	2.7 ± 0.8	3.3 ± 0.6	3.3 ± 0.7	3.2 ± 0.8	3.4 ± 0.8	3.4 ± 0.8¶	3.5 ± 0.7¶
- vigilance (↑)	1-4	2.6 ± 0.8	2.4 ± 0.9	3.2 ± 0.8	3.3 ± 0.8	3.3 ± 0.8	3.3 ± 0.9	3.4 ± 0.9¶	3.5 ± 0.7¶
- intimate relationships & sexual activity†(↓)	1-4	2.6 ± 1.0	2.9 ± 1.0	2.9 ± 1.1	3.1 ± 1.1	3.0 ± 1.2	2.4 ± 1.6	2.3 ± 1.5	2.8 ± 1.5
- total score (↑)		13.7 ± 3.1	13.9 ± 3.7	16.6 ± 2.8	16.7 ± 3.1	16.4 ± 3.6	16.3 ± 3.6	16.3 ± 3.6¶	17.1 ± 3.1¶
Medical outcomes study 36-item short-form health survey									
- physical functioning (↑)	0-100	71 ± 23	67 ± 24	79 ± 22	81 ± 19	84 ± 17	84 ± 17	87 ± 17¶	79 ± 23¶
- social functioning (↑)	0-100	66 ± 23	69 ± 24	80 ± 21	79 ± 21	76 ± 24	76 ± 24	79 ± 27¶	85 ± 20¶
- role physical (↑)	0-100	25 (0–75)	25 (0–100)	100 (25–100)	100 (44–100)	100 (13-100)	100 (13-100)	100 (88-100)‖	100 (25-100)‖
- role emotional (↑)	0-100	100 (33–100)	100 (33–100)	100 (67–100)	100 (59–100)	100 (0-100)	100 (0-100)	100 (67-100)	100 (100-100)
- mental health (↑)	0-100	71 ± 18	68 ± 18	77 ± 17	75 ± 16	71 ± 22	71 ± 22	78 ± 20	78 ± 16¶
- vitality(↑)	0-100	39 ± 19	39 ± 22	64 ± 21	61 ± 20	62 ± 24	62 ± 24	63 ± 24¶	63 ± 22¶
- bodily pain (↑)	0-100	75 ± 27	78 ± 26	80 ± 27	82 ± 24	85 ± 22	85 ± 22	85 ± 22¶	80 ± 23
- general health perception (↑)	0-100	58 ± 21	55 ± 23	65 ± 21	61 ± 23	67 ± 23	67 ± 23	67 ± 20¶	59 ± 23

* Plus-minus values are means ± standard deviations; values with additives in parenthesis are medians with interquartile ranges. Neurobehavioral outcomes at all follow-up time-points were compared by Students' t-tests. For comparing neurobehavioral outcomes with skewed distributions, Mann-Whitney U test were used.

† At baseline this item was completed by 48 patients in the oral appliance group and by 47 patients in the CPAP group. At the two-month follow-up, this item was completed by 47 patients in the oral appliance group and by 46 patients in the CPAP group. At the one-year and two-year follow-up all patients completed this item.

‡ The arrows within parenthesis indicate the direction of improvement for each variable after two years of treatment compared to baseline.

‖ Significant difference ($p<0.05$) between baseline and the two-year follow-up values (Mann-Whitney U test).

¶ Significant difference ($p<0.05$) between baseline and the two-year follow-up values (paired Student's t-test).

Abbreviations: CPAP = continuous positive airway pressure.

Discussion

The results of this study indicate that, regarding treatment success, there is no significant difference between oral appliance therapy and CPAP in treating mild-to-severe OSAS in a two-year follow-up. CPAP, however, showed a tendency towards a higher (non-significant) overall success rate than oral appliance therapy. This tendency was most pronounced in patients with severe OSAS. Both therapies had positive effects on polysomnographic variables during the follow-up but CPAP therapy was significantly more effective in lowering the AHI and in improving minimal oxygen saturation levels at the one- and two-year follow-up. In this study, more people (not significant) dropped out in the oral appliance group compared to the CPAP group as they were considered nonadherent or nonsuccessful. Both treatments seemed to be comparable in improving subjective sleepiness, functional outcomes and health perceptions.

To our knowledge this is the first follow-up of an RCT, comparing the two-year outcome of oral appliance- and CPAP therapy in patients with mild-to-severe OSAS. From this present follow-up study, short-term (2 months) results have previously been described (5), concluding that the outcome (in terms of proportions of successful treatments) of oral appliance therapy was not inferior to CPAP therapy. In that study, sub-group analysis showed a tendency towards a higher, but not significant success rate of oral appliance therapy in patients with non-severe OSAS (AHI 5-30) compared with CPAP (84.0% versus 80.0%). The follow-up of these patients, as described in this study, shows that CPAP therapy generally yielded more successful treatments (not significant difference of 14.4%) after two years of therapy. This difference can first be explained by the fact that we included patients with severe OSAS. In a systematic review (4) it is described that CPAP is more effective than oral appliance therapy in reducing respiratory disturbances, especially in patients with moderate and severe OSAS. Secondly, patients switched to the alternative therapy because of adherence problems or nonsuccess of their treatment after the two-month follow-up. Several studies indentified specific predictors for treatment success with oral appliance therapy (20-22). A lower baseline AHI, lower BMI and younger age were all associated with better treatment responses to oral appliance therapy. In this follow-up study, seven patients who were older, more obese and with predominantly severe OSAS, switched from oral appliance therapy to CPAP therapy because oral appliance therapy appeared to be nonsuccessful. More obese patients show an enlargement of upper airway adipose tissue, assessed by magnetic resonance imaging (23, 24). It was found that mandibular advancement increases the retropalatal airway space in non-obese, but not in obese patients (25). This may explain why the above-mentioned 7 patients were not treated successfully with an oral appliance. Notwithstanding this outcome, oral-appliance therapy was still successful in 50.0% of the patients with severe OSAS who completed the two-year follow-up. According to the latest practice parameters of the American Academy of Sleep (26), an oral appliance is indicated in patients with mild-moderate OSAS who

- prefer an oral appliance to CPAP
- do not respond to CPAP
- are unsuitable candidates for CPAP

- who fail treatment attempts with CPAP.

However, our results indicate that an oral appliance can also play an important role in treating specific patients with severe OSAS in the long-term.

Oral appliance therapy had a tendency to be less stable during the two-year follow-up, resulting in more dropouts compared to CPAP therapy. This finding is consistent with other studies, showing deterioration in success with oral appliance therapy, even in patients who were treated effectively in the short-term (7, 8, 10). We currently assume that the working mechanism of an oral appliance is based on advancement of the mandible and its attached soft tissue structures and musculature, especially the genioglossus muscle, resulting in an increased tone with increased anteroposterior and lateral dimensions of the upper airway (27, 28). Bearing the above-mentioned considerations in mind, this deterioration in treatment success is possible due to loosening and adaptation of soft tissue structures and musculature of the upper airway as a result of long-term overnight mandibular advancement. It could be hypothesized that patients with more severe OSAS need to protrude the mandible more extensively to gain the desired effect, with in the long term, a possible overstretching which negatively affects the morphology of the upper airway soft tissue structures and tonus of the musculature. Furthermore, it has been described that the muscle tone of the genioglossus is negatively correlated with age (29). Therefore, a second explanation is that the increasing age of our study group results in a decreased success of oral appliance therapy. It is unknown to what extent both possibilities contribute to this change in outcome.

Subjective improvements in sleepiness, functional outcomes and health perceptions were found in both treatment groups (no significant differences), underlining the therapeutic success of oral appliance and CPAP therapy at all time-points during the follow-up, even in patients with severe OSAS. Similar findings in different studies using the same questionnaires (pooled) were reported in a review article by Chan and co-workers (30). However, most of these studies included only mild and moderate OSAS patients.

The present study has some potential limitations. Patients were allowed to switch therapy during the follow-up if they were considered nonadherent or if treatment was considered nonsuccessful. This may have biased our results because patients could pretend to be nonadherent after randomization in a possible non-preferred study group. However, only small numbers of patients switched, and except for one patient, all patients switched after two months of therapy. We also believe that a serious disorder, such as OSAS, should be treated as effective as possible and the possibility to switch during the follow-up period provides a better picture of the true clinical situation. We furthermore considered all patients who discontinued treatment for any reason as dropout, even if they were treated effectively (worst-case-scenario). Success rates therefore may be underestimated.

Another limitation is the sample size that was determined for the two-month RCT (5). There was a priori risk of having ended up with an insufficient number of patients for reliable long-term results as dropouts in the long term were not anticipated in the power-analysis. Future studies should therefore focus and power on the long-term outcome of both oral appliance- and CPAP therapy in pre-stratified treatment groups.

In conclusion, regarding the percentage of successful treatments, no significant differences were found between oral appliance therapy and CPAP in treating mild-to-severe OSAS in a two-year follow-up. However, CPAP was more effective in lowering the AHI and showed higher minimal oxygen saturation levels compared to oral appliance therapy. Furthermore it shows a tendency to be more successful in severe OSAS patients. Though, even in a two-year follow-up, oral appliance therapy seems a viable alternative to CPAP in the treatment of mild and moderate OSAS. Oral appliances may be considered as a long-term alternative in severe OSAS patients who do not respond to CPAP or who fail treatment attempts with CPAP. Further research with larger groups of patients is needed to investigate which specific patients with severe OSAS are treated successfully with an oral appliance.

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CHAPTER 4

Long-term adverse effects of oral appliance therapy

CHAPTER 4.1

Long-term oral appliance therapy in obstructive sleep apnoea syndrome; a cephalometric study on craniofacial changes

This chapter is an edited version of:
Doff M.H.J., Hoekema A, Pruim G.J., Huddleston Slater J.J.R., Stegenga B. Long-Term Oral Appliance Therapy in Obstructive Sleep Apnea: a Cephalometric Study of Craniofacial Changes.
J Dent 2010; 38:1010-1018

Abstract

The aim of this controlled study was to cephalometrically assess possible changes in craniofacial morphology associated with long-term use of an adjustable oral appliance compared with continuous positive airway pressure (CPAP) in patients with the obstructive sleep apnoea syndrome (OSAS). In addition, we wanted to study the relationship between these possible changes and the degree of mandibular protrusion associated with oral appliance therapy.

Fifty-one patients were randomized to oral appliance therapy and fifty-two patients to CPAP therapy. At baseline and after follow-up (2.3 ± 0.2 years), a lateral cephalogram of all patients was made in maximum intercuspation to determine relevant cephalometric variables. Both baseline and follow-up cephalograms were traced digitally whereupon cephalometric variables were compared. Changes in craniofacial morphology between the oral appliance- and CPAP group were evaluated with a linear regression analysis.

Compared with CPAP, long term use of an oral appliance resulted in small but significant (dental) changes. Overbite and overjet decreased, 1.0 (±1.5) mm and 1.7 (±1.6) mm, respectively. Furthermore we found a retroclination (-2.0 (± 2.8) degrees) of the upper incisors and a proclination (3.7 (± 5.4) degrees) of the lower incisors. Moreover, the lower- and total anterior facial height increased significantly, 0.8 (± 1.5) mm and 0.9 (± 1.4) mm, respectively. No changes in skeletal variables were found. Linear regression analysis revealed that the decrease in overbite was associated with the mean mandibular protrusion during follow-up (β = -0.029, SE = 0.014, $p<0.05$).

Oral appliance therapy should be considered as a life long treatment, and there is a risk of craniofacial changes to occur. Therefore, patients treated with an oral appliance, need a thorough follow-up by a dentist or dental-specialist experienced in the field of dental sleep medicine.

Introduction

The obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, characterized by disruptive snoring and repetitive partial or complete obstructions of the upper-airway (i.e. hypopnoeas and apnoeas, respectively) (1). The severity of the disorder is usually expressed by the apnoea-hypopnoea index (AHI), i.e., the mean number of apnoeas and hypopnoeas per hour of sleep. OSAS may be classified as mild (AHI 5-15), moderate (AHI 15-30), or severe (AHI >30) (2). As a result of the condition patients may suffer from excessive sleepiness, an increased risk of accidents, and an impaired quality of life. Furthermore, patients have an increased risk of ischemic heart disease, congestive heart failure, and stroke (3, 4).

For OSAS patients, continuous positive airway pressure (CPAP) is generally considered the treatment of choice (5). However, because of the obtrusive character of the device, patients may abandon therapy. An oral appliance aims at relieving upper airway obstructions during sleep by repositioning the mandible in a forward and downward position (6). Oral appliance therapy has been demonstrated to be effective especially in mild and moderate OSAS cases (7, 8). However, in severe OSAS cases, CPAP is still the treatment of first choice.

When commencing oral appliance therapy, side effects are commonly reported in the initial period of use. These usually transient and mild side effects include tooth pain, occlusal changes in the morning, dry mouth or excessive salivation, gum irritation, temporomandibular joint pain, temporomandibular joint sounds and myofascial pain (7, 9-16). Some authors report that some of these side effects can be more severe and continuous (17-20).

Craniofacial changes related to long-term oral appliance use have been studied with cephalometry (15, 17, 21-24). Reported long-term changes (2-3 yrs) in craniofacial morphology were generally related to the patient's dentition. Most studies found a significant decrease in overjet and overbite (9, 13, 15, 22-25). Furthermore a retroclination of the maxillary incisors, a proclination of the lower incisors (9, 13, 15, 23-25) and a more downward (17, 21, 22) and forward (22) position of the mandible have been reported. In the majority of these studies, however, a control group was absent. In addition, in most studies only patients with mild-to-moderate OSAS or asymptomatic snorers were included. Furthermore, all studies except for one (24) evaluated the effects of an oral appliance that was non-adjustable and fixed the mandible in a predefined position at 50-75% of the maximum mandibular protrusion. Therefore, the relationship between the amount of mandibular protrusion during follow-up and the extent of craniofacial changes is an aspect that needs further study.

The aim of the present study was to cephalometrically assess possible changes in craniofacial morphology associated with long-term use (2 yrs) of a titratable oral appliance and compared with a CPAP control group, in patients with mild to severe OSAS. Secondly, we studied the relationship between the occurrence of these changes and the degree of mandibular protrusion during oral appliance therapy.

Materials & Methods

Patient Selection

The effectiveness of an oral appliance compared with CPAP therapy for OSAS was evaluated in a separate randomized controlled trial (8). All patients in that study were recruited through the Department of Home Mechanical Ventilation of the University Medical Center Groningen, The Netherlands. Subjects over 20 years of age and diagnosed with OSAS (AHI > 5) based on polysomnography (2) were eligible, and if they obeyed predefined medical, psychological, and dental inclusion criteria, patients were randomized for either oral appliance- (n = 51) or CPAP therapy (n = 52) (Table 1).

For the present study, we assessed changes in the craniofacial morphology as a result of long-term oral appliance therapy in OSAS patients. After two years, 37 patients (including those who had switched) in the CPAP group and 31 patients (including those who had switched) in the oral appliance group completed the follow-up. Details of patient selection criteria for our study are provided in Figure 1. Patients randomized for oral appliance therapy who had switched to CPAP therapy were excluded if they had been using the appliance for more than 3 months. Patients who were *nonsuccessful* or *nonadherent* to treatment and patients who underwent upper airway surgery during the follow-up period were also excluded.

The present study was approved by the Groningen University Medical Center's Ethics Committee. Written informed consent was obtained from each patient before enrolment.

Study Design

At baseline, patients had been subjected to a polysomnographic evaluation, based on which they were classified as having non-severe (AHI ≥ 5 to 30) or severe (AHI > 30) OSAS. In all patients a digital lateral cephalogram was obtained at baseline to determine cephalometric variables related to the craniofacial morphology (23, 26-29). The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a forward and downward position. By turning a propulsion screw that was incorporated anteriorly in the appliance, patients could gradually adjust the mandibular advancement with 0.2 mm increments. The maximal range of mandibular protrusion was first determined with a George-Gauge™ (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at approximately 50% of the patient's maximum protrusion. After having accustomed to this protrusive position during a two-week period, patients were allowed to adjust the oral appliance during a 6-week period. When OSAS symptomatology (snoring, excessive daytime sleepiness, apnoeas and/or hypopnoeas) appeared to persist, patients were instructed to advance the mandible each night with 1 to 2 increments (i.e. 0.2-0.4 mm). Adjustment of the oral appliance was continued until symptoms had improved to the patient's satisfaction, or until further protrusion of the mandible resulted in discomfort.

CPAP-adjustment was performed during an afternoon nap. This technique, aimed at abolishing all signs of apnoeas, hypopnoeas and snoring, has been shown to be an appropriate procedure

for the effective adjustment of CPAP (30).

Following CPAP- and oral appliance adjustment, an eight week follow-up period was arranged that allowed for habituation and, if necessary, adjustment of CPAP or the oral appliance. After this period, a second polysomnographic study was performed. If polysomnography indicated an apnoea-hypopnoea index ≥5, CPAP or the oral appliance was further adjusted. A third polysomnographic study was performed 4 weeks after that adjustment.

Treatment was considered successful when the apnoea-hypopnoea index either was <5 or showed *substantial reduction*, (8) defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient without subjective OSAS-symptoms while using therapy. Patients, for whom oral appliance or CPAP therapy was successful, continued this treatment. If either treatment was not successful at any time during the follow-up period, patients were offered the alternative (CPAP or oral appliance, respectively) therapy, which was thereupon titrated in the same way as with the initial therapy.

After a two-year follow-up period all patients were subjected to a final polysomnographic evaluation and a second digital lateral cephalogram. The mean mandibular protrusion during the follow-up period (expressed as percentage of the maximum mandibular protrusion) was used for further analysis. The vertical dimension of the oral appliance was kept constant during the entire follow-up period. Both mandibular protrusion and mouth opening (including the vertical overbite) were measured with a digital sliding calliper with 0.01 mm accuracy. These measurements were carried out at baseline, after two months, one year and two years of treatment. At these intervals also other clinical measurements (weight, length, neck circumference and intoxications) were carried out.

The primary outcome measure was the change in craniofacial morphology, measured using cephalometric variables, between baseline and the final follow-up visit. Secondly the relationship between the mean mandibular protrusion during the follow-up and the magnitude of changes in the craniofacial morphology was studied.

Cephalometric analysis

All digital lateral cephalograms were recorded using a ProMax Cephalostat (Planmeca, Helsinki, Finland). The *mirror position* (31) was used in order to obtain a reproducible position of the head. Patients were instructed to swallow and close their mouth with the mandible in maximum intercuspation and the lips in a relaxed position. After a short period of relaxed tidal breathing the cephalogram was taken at end-expiration. Early morning visits were avoided because some patients were not able to close in maximum intercuspation at that time but were habituated to bite with the mandible in a more protrusive position.

A predefined trace-protocol (Table 2, Fig. 2) was used to perform all tracings using Viewbox software® (version 3.1.1.6, Dhal Software, Kifissia, Greece). To minimize identification error, one blinded observer (MD) performed all tracings. Furthermore, for sagittal and vertical measurements, superimposition was performed on the anterior contour of the sella turcica and sella-nasion (SN) (32). In order to further reduce the error of measurements, the coordinates of sella and

Table 1: Baseline characteristics of 103 patients treated with an oral appliance or CPAP.

Variable	Oral Appliance * (n=51)	CPAP* (n=52)
Male / female ratio	43 / 8	49/3
Age (years)	49 ± 10	49 ± 10
Body-mass index (kg/m^2)	32 ± 6	33 ± 6
Apnea-hypopnea index (no/hour)	39 ± 31	40 ± 28
Neck circumference (cm)	44 ± 4	45 ± 4
minSaO_2 (%)	78 ± 9	78 ± 10
OSAS severity	Non-severe: n=25 (49%) Severe: n=26 (51%)	Non-severe: n=25 (48%) Severe: n=27 (52%)

* Plus-minus values are means ± standard deviations.
Abbreviations: minSaO_2 = lowest oxyhemoglobin saturation during sleep, NS = not significant.

nasion were, after superimposition, transferred from the baseline to the follow-up cephalogram in order to obtain exactly the same coordinates on both cephalograms. All linear cephalometric measurements were corrected for a radiographic enlargement of 12%.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). All variables were normally distributed and their means and standard deviations (s.d.) are reported. The AHI of the oral appliance and CPAP patients at baseline was distributed normally after logarithmic transformation. To compare outcomes between cephalometric variables (intention-to-treat) at baseline and follow-up, paired Student's *t*-tests were performed. Although proper randomization is executed, a (small) difference in the average values of a determinant for the two treatment arms may occur. To correct for this regression-to-the-mean phenomenon statistically in our analysis, the baseline value was at all times included in the regression model.

For continuous cephalometric measures, 'between groups' effect sizes are reported as Cohen's *d*, the standardized mean difference, based on mean group change scores divided by the pooled standard deviation. The differences in craniofacial morphology between the oral appliance and CPAP group *d* reflect the net side-effects associated with oral appliance therapy, a measure that controls for spontaneous changes in the control group and pre-existing random group differences at baseline. Cohen's *d* effect sizes are interpreted as small (0.20), medium (0.50), or large (>0.80) (33).

For the oral appliance group, linear regression analysis was used to determine the relationship between the changes in craniofacial morphology and the mean mandibular protrusion during the follow-up period. A significance level of 0.05 was predefined in all cases.

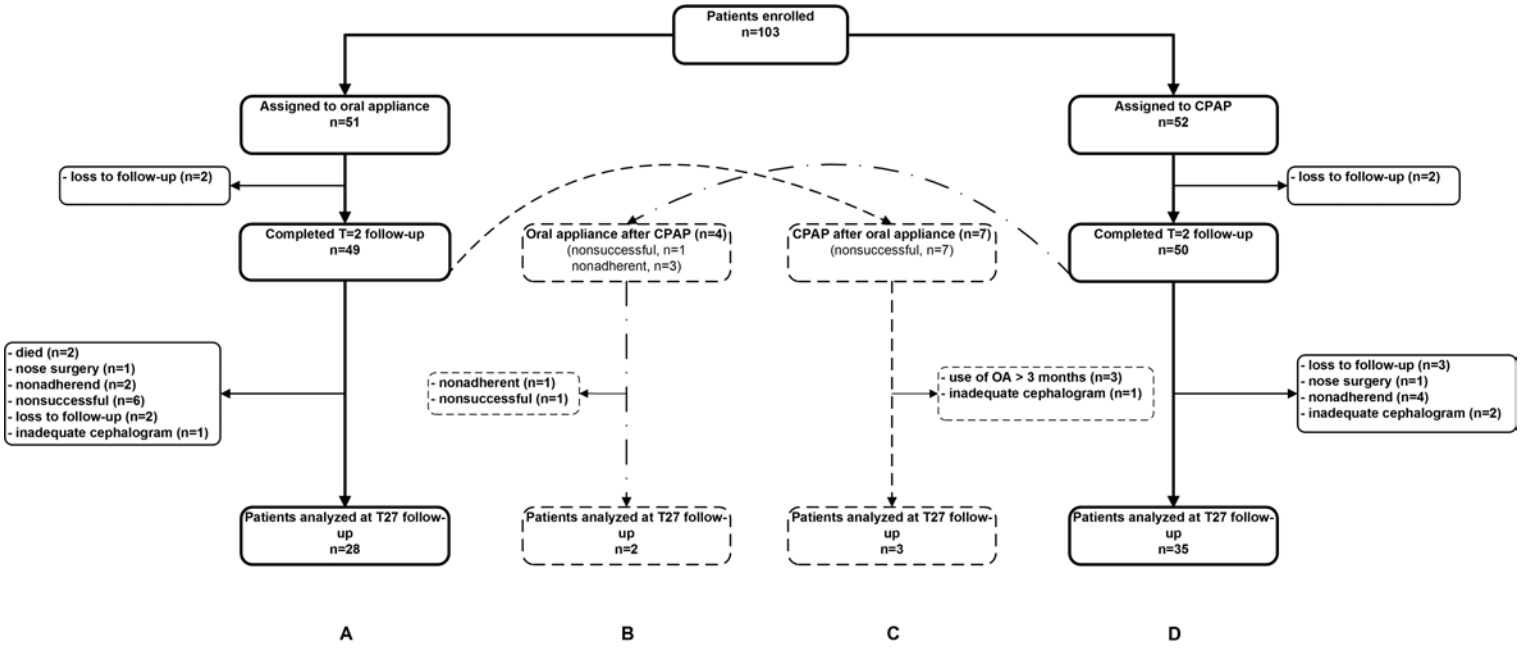

Figure 1. Flow diagram of the patient selection procedure.

* Patients who discontinued treatment for any reason were considered *nonadherent* to treatment.

† Treatment was considered effective when the apnoea-hypopnoea index was <5 or showed substantial reduction, defined as reduction in the index of at least 50% from the baseline value to a value of <20 in a patient without symptoms while using therapy. Patients not meeting these criteria were considered *nonsuccessful*.

Results

For analysis, 31 (group A+C) and 37 (group B+D) patients were included in the oral appliance group and the CPAP group, respectively (Fig. 1). The mean follow-up period was 2.3 (± 0.2) years in the oral appliance group (range 2.1-3.1 years) and 2.4 (± 0.3) years in the CPAP group (range 2.1-3.2 years).

In the oral appliance group, the mean mandibular protrusion during the follow-up period was 79 (± 20) % of the maximal mandibular protrusion. The mean mouth opening (including overbite) while wearing the oral appliance was 13 (± 3) mm.

Cephalometric analysis

In the oral appliance group, no significant changes were found in the variables pertaining to the base of the skull. Concerning maxillary measurements, the angle between the upper incisor line and the maxillary plane (Ui-MxP) decreased 2.0 (± 2.8) degrees as a result of long-term oral appliance therapy compared with CPAP therapy, indicating a retroclination of the maxillary incisors (Table 2).

Mandibular measurements showed that the position of the mandible in relation to the skull base, i.e. the SNB-angle, was reduced 0.4 (± 0.9) degrees and the angle between the lower incisor line and the mandibular plane (Li-MnP) increased 3.7 (± 5.4) degrees, indicating a proclination of the mandibular incisors. Furthermore, a downward and backward rotation of the mandible was observed, as the shortest linear distance from menton to line SN-perp (Me-hor) decreased 0.7 (± 1.6) mm and the shortest linear distance between menton and line SN (Me-ver) increased 0.7 (± 1.4) mm.

Regarding the intermaxillary relationships, the ANB-angle increased 0.3 (± 0.9) degrees and the interincisal angle (Ui-Li) decreased 2.3 (± 5.8) degrees. Furthermore, the overbite and overjet decreased 1.0 (± 1.5) mm and 1.7 (±1.6) mm, respectively.

Concerning facial height there was an increase in the lower anterior facial height (0.8 ± 1.5 mm) and the total anterior facial height (0.9 ± 1.4 mm), resulting in a decrease of the anterior facial height ratio (0.8 ± 1.9 percent). No significant changes were observed in any of the variables regarding the posterior facial heights.

When adjusted for regression-to-the-mean effects, our data show significant, mainly dental changes in the craniofacial morphology in the oral appliance group compared with the CPAP group following two years of treatment (Table 2, Fig. 3). A retroclination of the upper incisors (*d*=0.6) and a proclination of the lower incisors (*d*=0.7) was found, the overjet (*d*=1.3) and overbite (*d*=0.6) had decreased, and the lower anterior facial height (*d*=0.6) as well as the total anterior facial height (*d*=0.5) had increased in the oral appliance group compared with the CPAP group. Conversely, the anterior facial height ratio did not change significantly when comparing the oral appliance and CPAP group.

Linear regression analysis revealed that the decrease in overbite was significantly associated with the mean mandibular protrusion during follow-up (β=-0.029, SE=0.014, $p<0.05$). The control

Table 2: Cephalometric variables used in the study.

Variable	Oral Appliance* n = 31			CPAP* n = 37			Significance of the difference‡ (Cohen's *d*) ‖
	Baseline	Follow-up	Difference	Baseline	Follow-up	Difference	
Base of the skull							
Ba-S-N; the angle between the lines Ba-S and S-N (degrees)	48.8 ± 5.4	48.6 ± 5.3	-0.22 ± 0.7	47.7 ± 6.7	47.4 ± 6.7	-0.30 ± 1.1	NS
SN-length; distance between S and N (mm)	70.4 ± 3.4	70.5 ± 3.4	0.0 ± 0.2	69.8 ± 3.1	70.0 ± 3.2	0.3 ± 0.7	NS
Maxilla							
SNA (degrees)	79.2 ± 4.2	79.2 ± 4.3	-0.0 ± 0,5	80.3 ± 4.0	80.2 ± 4.1	-0.1 ± 0.6	NS
Ui-MxP; angle between the upper incisor line and the maxillary plane (degrees)	107.0 ± 8.1	105.0 ± 7.9	-2.0 ± 2.8†	114.1 ± 8.3	113.9 ± 8.3	-0.2 ± 3.1	p < 0.05 (0.6)
Maxillary length; distance between ans and pns (mm)	54.3 ± 4.3	54.4 ± 4.4	0.1 ± 1.1	53.9 ±3.7	53.8 ±3.5	-0.0 ± 1.7	NS
Mandible							
SNB (degrees)	75.2 ± 3.9	74.8 ± 4.2	-0.4 ± 0.9†	77.7 ± 3.9	77.5 ± 3.9	-0.2 ± 1.0	NS
Li-MnP; angle between the lower incisor line and the mandibular plane (degrees)	102.2 ± 7.4	105.9 ± 8.2	3.7 ± 5.4†	102.1 ± 9.3	102.6 ± 9.1	0.6 ± 3.0	p < 0.05 (0.7)
MnP-SN; angle between the mandibular plane and SN-line (degrees)	34.3 ± 7.1	34.7 ± 6.8	0.4 ± 1.1	31.7 ± 6.3	31.9 ± 6.1	0.2 ± 1.4	NS
Ramus length; distance between Arm and Go (mm)	51.6 ± 6.7	51.7 ± 7.0	0.1 ± 1.6	55.0 ± 5.8	54.5 ± 5.7	-0.5 ± 1.6	NS
Body length; distance between Go and Me (mm)	66.9 ± 5.2	66.8 ± 5.6	-0.1 ± 1.7	68.5 ± 5.4	68.4 ± 4.9	-0.1 ± 2.9	NS
Mandibular length; distance between Arm and Me (mm)	102.8 ± 7.3	102.9 ± 6.8	0.1 ± 1.4	107.0 ± 5.3	106.7 ± 5.3	-0.3 ± 2.0	NS
Me-hor; shortest linear distance from Me to line SN-perp (mm)	31.6 ± 9.6	30.9 ± 9.7	-0.7 ± 1.6†	37.6 ± 8.2	37.3 ± 8.3	0.3 ± 2.6	NS
Me-ver; shortest linear distance from Me to line SN (mm)	118.0 ± 6.9	118.7 ± 6.6	0.7 ± 1.4†	118.7 ± 6.3	118.7 ± 6.3	0.0 ± 1.5	NS
Arm-hor; shortest linear distance from Arm to line SN-perp (mm)	16.9 ± 3.0	17.0 ± 3.3	0.1 ± 1.4	15.6 ± 3.1	15.8 ± 3.4	0.2 ± 1.2	NS
Arm-ver; shortest linear distance from Arm to line SN (mm)	27.8 ± 3.3	28.0 ± 3.2	0.2 ± 0.8	26.1 ± 3.4	26.4 ± 3.6	0.3 ± 1.2	NS

Table 2: Continued.

Intermaxillary relationships							
ANB; angle between the lines NA and NB (degrees)	4.0 ± 1.9	4.3 ± 2.2	0.3 ± 0.9†	2.5 ± 3.1	2.6 ± 2.8	0.1 ± 0.9	NS
Ui-Li (interincisal angle); angle between the lines Ui and Li (degrees)	124.8 ± 10.8	122.5 ± 10.9	-2.3 ± 5.8†	120.4 ± 13.4	119.7 ± 13.0	-0.6 ± 0.7	NS
Overbite; linear dimension measured from the most mesial point of the upper central incisor edge to the perpendicular projection on the buccale surface of the lower central incisor (mm)	2.4 ± 2.4	1.4 ± 2.4	-1.0 ± 1.5†	1.8 ± 2.3	1.5 ± 2.1	-0.2 ± 1.2	p < 0.05 (0.6)
Overjet; linear distance measured from the buccal surface of the lower central incisor to the projected point of the incisal edge of the upper central incisor (mm)	4.4 ± 2.2	2.8 ± 2.6	-1.7 ± 1.6†	3.3 ± 2.9	3.5 ± 2.8	0.2 ± 1.3	p < 0.05 (1.3)
Facial height							
Upper anterior facial height; distance between N and MxP along line N-Me (mm)	53.4 ± 3.7	53.5 ± 3.5	0.0 ± 0.5	52.5 ± 3.0	52.6 ± 2.8	0.1 ± 0.6	NS
Lower anterior facial height; distance between MnP and MxP along line N-Me (mm)	71.2 ± 5.7	72.0 ± 5.7	0.8 ± 1.5†	70.7 ± 5.0	70.8 ± 4.9	0.1 ± 0.6	p < 0.05 (0.6)
Total anterior facial height; distance between N and Me (mm)	124.6 ± 7.6	125.4 ± 7.4	0.9 ± 1.4†	123.2 ± 6.7	123.4 ± 6.4	0.2 ± 1.4	p < 0.05 (0.5)
Anterior facial height ratio; ratio between the upper anterior facial height and the lower anterior facial height (percent)	75.5 ± 7.1	74.6 ± 6.8	-0.8 ± 1.9†	74.6 ± 5.6	74.6 ± 5.6	0.1 ±1.7	NS
Upper posterior facial height; distance between S and MxP along line S-Go (mm)	42.9 ± 4.4	43.2 ± 4.5	0.3 ± 1.0	42.3 ± 3.6	42.4 ± 3.7	0.1 ± 0.8	NS
Lower posterior facial height; distance between Go and MxP along line S-Go (mm)	39.2 ± 7.0	39.3 ± 7.3	0.1 ± 2.2	40.9 ± 5.6	40.7 ± 5.7	-0.2 ± 1.4	NS
Total posterior facial height; distance between S and Go (mm)	82.1 ± 8.0	82.5 ± 7.9	0.4 ± 1.6	83.3 ± 6.2	83.1 ± 6.4	-0.2 ± 1.3	NS
Posterior facial height ratio; ratio between the upper posterior facial height and the lower posterior facial height (percent)	113.1 ± 23.7	114.2 ± 26.8	1.1 ± 10.2	105.4 ± 17.9	106.2 ± 18.2	0.8 ± 5.1	NS
Facial height ratio; ratio between the total posterior facial height and the total anterior facial height (percent)	65.9 ± 5.4	65.8 ± 5.3	-0.1 ± 1.0	67.7 ± 5.0	67.4 ± 5.1	-0.2 ± 1.3	NS

* Plus-minus values are means ± standard deviations.
† $p < 0.05$.
‡ After regression to the mean analysis.
|| Cohen's ***d*** is the standardized mean difference between the oral appliance group and the CPAP group.

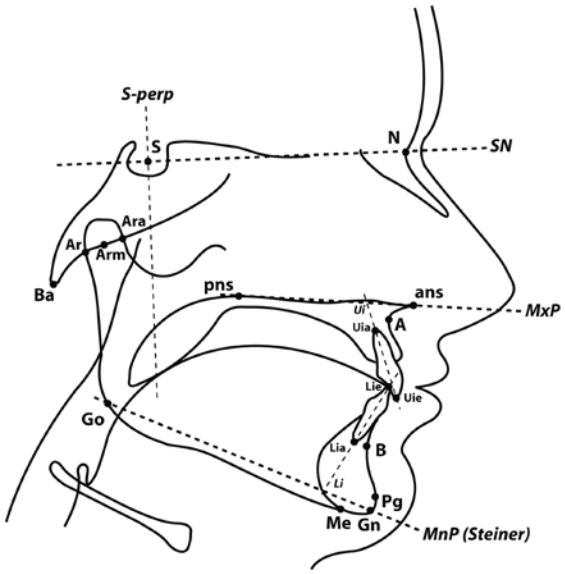

Figure 2. Cephalometric landmarks and reference lines traced on lateral cephalograms.

The following eighteen reference points were identified on lateral cephalograms: A (point A: the deepest midline concavity on the anterior maxilla), ans (anterior nasal spine: the tip of the median, sharp bony process of the maxilla at the lower margin of the anterior nasal opening), Ara (Anterior articulare: the point of intersection of the inferior cranial base surface and the averaged anterior surfaces of the mandibular condyles), Arm (Articulare midpoint; the midpoint of the line between Aa-Ar), Ar (articulare; the point of intersection of the inferior cranial base surface and the averaged posterior surfaces of the mandibular condyles), B (point B: the deepest midline concavity on the mandibular symphysis), Ba (Basion; the median point of the anterior margin of the foramen magnum, Gn (gnathion: the most anterior-inferior point on the contour on the bony chin symphysis, determined by bisecting the angle formed by the mandibular plane and a line through pogonion and nasion), Go (gonion: the constructed point of the intersection of the ramus plane and the tangent to the body of the mandible), Lia (lower incisor apex), Lie (lower central incisor edge: the incisal tip of the mandibular central incisor), Me (menton: the intersection of the bony inferior symphysis with the inferior margin of the mandibular body), N (nasion: the most anterior point on the frontonasal suture), Pg (pogonion: the most anterior point on the contour of the bony chin, determined by a tangent through nasion), pns (posterior nasal spine: the intersection of a continuation of the anterior wall of the pterygopalatine fossa and the floor of the nose, marking the dorsal limit of the maxilla), S (sella; the midpoint of the pituitary fossa), Uia (upper incisor apex), Uie (upper incisor incisal edge: the incisal tip of the maxillary central incisor).

The following six reference lines were identified on lateral cephalograms: Li (lower incisor line: the line through the lower incisor apex and the lower incisor incisal edge), MnP (mandibular plane according to Steiner: the line through gonion and gnathion), MxP (Maxillary plane: the line through the posterior nasal spine (pns) and the anterior nasal spine (ans)), SN (sella-nasion line: the line through sella and nasion), SN-perp (SN-perpendicular: the line through Sella (S) perpendicular on line SN), Ui (upper incisor line: the line through the upper incisor apex and the upper incisor incisal edge).

(CPAP) group did not reveal any significant changes in the craniofacial morphology after two years of treatment.

Discussion

To our knowledge, this is the first study in which changes in craniofacial morphology as a result of long-term oral appliance therapy are evaluated in a controlled study concerning patients from the full OSAS spectrum. The results of this study indicate that changes in craniofacial morphology should be anticipated in OSAS patients using an oral appliance for two years when compared with CPAP therapy. These changes, however, were predominantly dental in nature. Furthermore, by using linear regression analysis, an association was observed between the mean mandibular protrusion during the follow-up period and the decrease in overbite.

Changes in overbite and overjet, retroclination of the upper incisors and a proclination of the lower incisors have also been described in previous studies (9, 15, 23, 24). These changes have been attributed to a labially directed force to the mandibular incisors and a palatally directed force to the maxillary incisors while the appliance is in place and the mandible attempts to return to a less constrained position. Conversely, Ringqvist and co-workers (21) did not find significant changes in overbite, overjet, and inclination of the upper or lower incisors after two years of oral appliance use. A first explanation for this erratic result could be the different design of the oral appliance used in their study. The frontal parts of both tooth arches were not covered by acrylate. Therefore, the palatally and labially directed forces were not applied directly to the upper and lower incisors, respectively. Another explanation could be the degree of mandibular protrusion of 50% while wearing the oral appliance. Both explanations seem viable but it is unclear to what extent each of these possibilities contributes to the observed differences.

Protrusive positions of the mandible over 75% of the patient's maximum were applied in some patients in the present study. This could be explained by the fact that patients with mild, moderate, and severe OSAS were included. Severe OSAS patients may need more pronounced protrusive positions of the mandible in order to experience sufficient benefit from the oral appliance. Ringqvist et al (21) only included patients with mild-to-moderate disease. As dose dependency of oral appliance therapy has previously been described (34), it is conceivable that the oral appliance in this category is already effective in a less protrusive position, resulting in less severe dental side-effects.

In the oral appliance group, we found a backward (decreased Me-hor) and downward (increased Me-ver) rotation of the mandible, resulting in small but significant increases in the lower and total anterior facial heights, but not in the anterior facial height ratio. These findings corroborate the results from previous studies (17, 23, 24). It could be hypothesized that over-eruption of the molars, caused by possible inadequacies in the oral appliance's fit during follow-up, results in an increase in anterior facial height. However, in the present study the quality and fit of the oral appliances was checked annually and adjusted if required. Therefore, it seems unlikely that this mechanism explains the increase in the lower and total anterior facial heights in our study. The

small increase in anterior facial height is most likely the result of oral appliance-induced dental changes. The retroclination of the upper incisors and the proclination of the lower incisors result in a downward rotation of the mandible through incisal guidance, most likely resulting in a small but significant increase in the total and lower anterior facial height (35).

Bondemark (22) found an increase in mandibular length after two years of oral appliance use. We did not observe any significant changes in mandibular length (Arm-Me), ramus length (Arm-Go) or mandibular body length (Go-Me) in our patients. This discrepancy could be explained by the differences in mandibular landmarks used. Bondemark used the linear distance between condylion (Cd) and pogonion (Pg). We calculated mandibular length as the linear distance between articulare midpoint (Arm) and menton (Me). Pogonion could be an unreliable landmark if rotation of the mandible occurs, because the most anterior point of the mandibular symphysis will be displaced. However, menton is an anatomical landmark rather than a constructed landmark and, therefore, is more reliable when mandibular rotation is to be expected. Furthermore, it has been suggested that articulare is more reproducible than condylion on cephalograms exposed in habitual occlusion (36). We constructed the landmark articulare midpoint (Arm) as we hypothesized that this point is less susceptible to displacement when rotation of the mandible occurs (37).

It could be hypothesized that the long-term use of CPAP causes changes in the dental or skeletal morphology as a result of its tight-fitting (mouth-) nose mask. However, in the present study we did not find any changes in either dental- or skeletal variables in the CPAP group. Therefore, in retrospect the CPAP group appeared to be adequate as a control group.

In this study an adjustable oral appliance was used. The regression analysis showed that there appears to be an association between the decrease in overbite and the extent of mandibular protrusion. Therefore, it appears to be of importance to keep the mandibular protrusion associated with oral appliance use to a minimum. This finding may become increasingly important, as with increasing age OSAS symptomatology may worsen in patients who require a more extended protrusive mandibular position. It could be hypothesized that the extent of dental side effects might be more pronounced with adjustable appliances as there is a risk of advancing the mandible beyond an optimum position. As a result of including severe OSAS patients in this study, the mean mandibular protrusion might be larger in the present sample when compared with other studies that only studied patients with mild-moderate OSAS or snorers without OSAS.

Martinez-Gomis and co-workers (38) found a significant reduction in the number of posterior occlusal contacts after two years use of oral appliance. This tendency however, reversed during the period of 2 to 5 years of treatment. Therefore it seems viable that most dental changes occur during the first years of treatment with an oral appliance but tend to stabilize over time.

Inter- and intraobserver reliability measurements were not carried out in this study. However, in a recent study (26), interclass correlation coefficients (ICCs) were calculated for two experienced observers (MD and GP) after digital tracings using Viewbox 3.1.1.6 software®. Except for one, all ICCs were considered excellent (range 0.69-0.97).

Notwithstanding the fact that this study was prospective in design, the randomization and sample size calculation were performed based on the primary outcome measure for the randomised

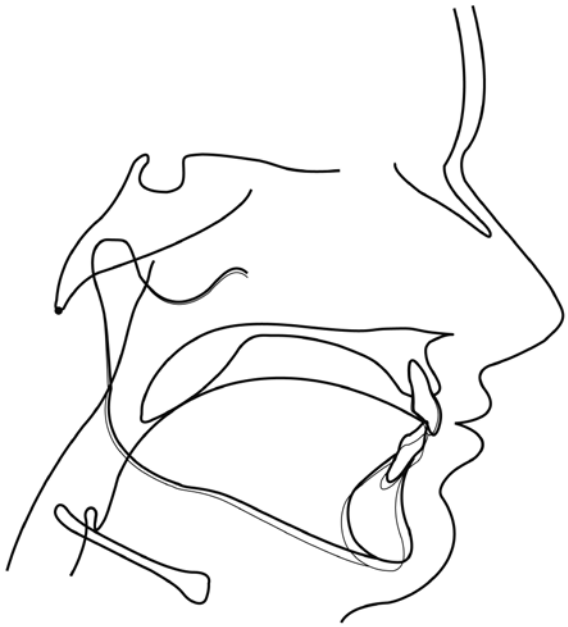

Figure 3. Craniofacial changes represented in an overall tracing, before (thick line) and after (thin line) oral appliance therapy.

controlled trial by Hoekema and co-workers (8). A post-analysis power calculation, using the change in overjet as clinical most important outcome variable, yielded a power of 88% (n1=31, n2=37, α=0.05).

In conclusion, our results show that the long-term use of an oral appliance causes predominantly dental changes in the craniofacial morphology in OSAS patients. All effect sizes of the observed significant changes, expressed as Cohen's *d*, were medium-to-large and should be considered as clinically important. Nevertheless, a disorder with serious cardiovascular consequences should be treated as effective as possible. This supersedes the maintenance of a patients' baseline craniofacial morphology. Discontinuation of oral appliance therapy because of the development of craniofacial side-effects should only be considered in patients who are able to tolerate or accept another effective treatment modality for the OSAS. However, in agreement with Almeida and co-workers (24), we endorse the importance of collecting clinical data as cast-models and intra-oral photographs before and during treatment with an oral appliance. Thus, patients treated with an oral appliance need a thorough follow-up by a dentist or dental-specialist experienced in the field of dental sleep medicine.

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CHAPTER 4.2

Long-term oral appliance therapy in obstructive sleep apnoea syndrome; a controlled study on dental side-effects

This chapter is an edited version of:

Doff M.H.J., Finnema K.J., Hoekema A, Wijkstra P.J., de Bont L.G.M., Stegenga B. Long-Term Oral Appliance Therapy in Obstructive Sleep Apnoea Syndrome: a Controlled Study on Dental Side-Effects. *Clin Oral Investig* 2012 (accepted)

Abstract

The objectives of this study were to assess possible dental side-effects associated with long-term use of an adjustable oral appliance compared with continuous positive airway pressure (CPAP) in patients with the obstructive sleep apnoea syndrome (OSAS) and to study the relationship between these possible side-effects and the degree of mandibular protrusion associated with oral appliance therapy.

As part of a previously conducted randomized controlled trial, 51 patients were randomized to oral appliance therapy and 52 patients to CPAP therapy. At baseline and after a two-year follow-up, dental plaster study models in full occlusion were obtained which were thereupon analyzed with respect to relevant variables.

Long term use of an oral appliance resulted in small but significant dental changes compared with CPAP. In the oral appliance group, overbite and overjet decreased, 1.2 (±1.1) mm and 1.5 (±1.5) mm, respectively. Furthermore, we found a significantly larger anterior-posterior change in the occlusion (-1.3 ± 1.5 mm) in the oral appliance group compared to the CPAP group (-0.1 ± 0.6 mm). Moreover, both groups showed a significant decrease in number of occlusal contact points in the (pre)molar region. Linear regression analysis revealed that the decrease in overbite was associated with the mean mandibular protrusion during follow-up (Regression coefficient (β)= -0.02, 95% Confidence Interval (CI) (-0.04 to -0.00)).

Oral appliance therapy should be considered as a life long treatment, and there is a risk of dental side-effects to occur. Therefore, patients treated with an oral appliance, need a thorough follow-up by a dentist or dental-specialist experienced in the field of dental sleep medicine.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is characterized by repetitive episodes of pharyngeal collapse with increased airflow resistance during sleep (1) and is often accompanied by extensive snoring. OSAS is associated with excessive daytime sleepiness (EDS), (sexual) dysfunction, neurocognitive deficits and higher rates of cardiovascular and cerebrovascular morbidity and mortality (2-5). In the North-American population, OSAS affects approximately 4% of the male and 2% of the female adults (4). Severity of the disorder is usually expressed by the apnoea-hypopnoea index (AHI), i.e. the mean number of apnoeas and hypopnoeas per hour of sleep and is classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30) (6). Standard treatment with Continuous Positive Airway Pressure (CPAP) is highly efficacious for OSAS but adherence to the treatment limits its overall effectiveness (7). Oral appliance therapy is a viable alternative in the treatment of OSAS, especially in the mild and moderate cases and in patients unwilling or unable to tolerate CPAP (8). Generally, oral appliances aim at enlarging the upper airway during sleep by holding the mandible in a forward and downward position (9).

Mild and 'transient' side-effects are commonly reported in the initial period of oral appliance therapy and include tooth pain, temporomandibular joint (TMJ) pain, myofascial pain, dry mouth, excessive salivation, and gum irritation (10-18). In several studies, dental side-effects related to long-term use of an oral appliance have been studied with study model analysis (16, 19-22). However, most of these studies were retrospective, comprised small study samples, did not include a control group or only included snorers or mild and moderate OSAS patients. Furthermore, all studies except for two (21, 22) evaluated the effects of an oral-appliance that was nonadjustable and fixed the mandible in a predefined position at 50–75% of the maximum mandibular protrusion. Therefore, the relationship between the amount of mandibular protrusion during follow-up and the extent of dental side-effects is an aspect that needs further study.

The objectives of this parallel controlled follow-up study were to assess:

1. the occurrence of dental side-effects following long-term (2 yrs) oral appliance therapy compared with CPAP in a prospective study in patients with mild-to-severe OSAS.
2. the relationship between the mean mandibular protrusion and the degree of dental side-effects to occur.

Materials & Methods

Patient Selection

The efficacy of an oral appliance in the treatment of OSAS, compared with CPAP, has been evaluated in a previously executed randomized controlled trial (23). The materials and methods of this specific study are briefly summarized below. All patients were recruited through the Department of Home Mechanical Ventilation of the University Medical Center Groningen, the Netherlands. Subjects over 20 years of age and diagnosed with OSAS (apnoea-hypopnoea index (AHI) > 5) based on polysomnography (6) were eligible. If patients fulfilled predefined medical, psychologi-

cal, and dental inclusion criteria, they were selected for the study and subsequently randomized for either oral appliance (n=51) or CPAP therapy (n=52).

For the present study, we assessed dental side-effects in the group of patients treated with an oral appliance compared to those treated with CPAP. Patients considered *nonsuccessful* or *nonadherent* (23) were offered to switch to the alternative therapy at any time during the follow-up. Patients that switched from oral appliance therapy to CPAP or vice versa were excluded from analysis. Furthermore, patients were excluded if they received upper airway surgery during follow-up or if the oral appliance was used <5 nights a week or <5 hours per night. Details of patient selection criteria for our study are provided in figure 1.

The present study was approved by the Groningen University Medical Center's Ethics Committee (METc2002/032). Written informed consent was obtained from each patient before enrolment.

Study design

At baseline, patients had been subjected to a polysomnographic evaluation, based on which they were classified as having non-severe (AHI 5–30) or severe (AHI >30) OSAS. From all patients, dental plaster study models were obtained at baseline and after two years of treatment to determine variables related to the dental morphology and the (dental) occlusion. The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a forward and downward position. This type of an oral appliance is often referred to as a Mandibular Repositioning Appliance (MRA). By turning a propulsion screw that was incorporated anteriorly in the appliance, patients could adjust the mandibular advancement with 0.2 mm increments with each turn. The maximum range of mandibular protrusion was first determined with a George-Gauge™ (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at 50% of the patient's maximum protrusion. After having accustomed to this protrusive position during a two-week period, patients were allowed to further adjust the oral appliance during a 6-week period. When subjective OSAS symptomatology (6) appeared to persist, patients were instructed to advance the mandible each night with 1 to 2 increments (i.e. 0.2-0.4 mm). This adjustment period had extended until symptoms were adequately improved or until further protrusion of the mandible resulted in discomfort. The mean mandibular protrusion during the follow-up period (expressed as percentage of the maximum mandibular protrusion) was used for further analysis. The vertical dimension of the oral appliance was kept constant during the entire follow-up period. Both mandibular protrusion and mouth opening (including the vertical overbite) imposed by the oral appliance were measured with a digital sliding calliper. These measurements were carried out at baseline, after two months, one year and two years of treatment. At these time-points, also other clinical measurements (weight, length and neck circumference) were carried out. At baseline and after two years of treatment, dental plaster study models in full occlusion were obtained for all patients.

CPAP-titration was performed during an afternoon nap. This technique, aimed at abolishing all signs of apnoeas, hypopnoeas and snoring, has been shown to be an appropriate procedure for

Table 1. Baseline characteristics, therapeutic use and cast analysis of patients who completed the two-year follow-up.

Variable	Oral Appliance * (n=29)	CPAP* (n=34)	Difference (p-value)‡
Age (years)	49.7 ± 8.9.	50.6 ± 10.1	NS
Male/female ratio	22/7	32/2	NS‖
Apnoea-Hypopnoea Index (no/hour)	35.6 ± 22.3	44.2 ± 27.9	NS
Body-mass index (kg/m^2)	31.4 ± 5.7	33.7 ± 5.7	NS
Therapeutic use : - nights per week - hours per night	 6.9 ± 0.4 7.1 ± 0.8	 6.7 ± 1.1 6.7 ± 1.3	 NS NS
Number of teeth (no): - upper arch - lower arch	 12.7 ± 1.5 13.1 ± 1.4	 13.1 ± 1.8 13.0 ± 1.5	 NS NS
Occlusal contact points cuspid-incisor region (no): - baseline - follow-up - difference (p-value)‡	 2.5 ± 1.7 2.2 ± 1.8 NS	 3.2 ± 2.0 3.0 ± 1.9 NS	 NS NS
Occlusal contact points (pre)molar region (no): - baseline - follow-up - difference (p-value)‡	 6.8 ± 2.6 5.1 ± 2.3 p<0.00	 6.9 ± 2.6 6.4 ± 2.3 p=0.03	 NS NS
Delta overbite (mm)	-1.2 ± 1.1	-0.1 ± 0.6	p<0.00
Delta overjet (mm)	-1.5 ± 1.5	-0.2 ± 0.7	p<0.00
Anterior-posterior movement (mm)	-1.3 ± 1.5	-0.1 ± 0.6	P<0.00

* values are means ± standard deviations.
† unpaired t-test.
‡ paired t-test.
‖ Fischers' exact test.
Abbreviations: CPAP = Continuous Positive Airway Pressure, NS = not significant.

the effective titration of CPAP (24).

Following CPAP- and oral appliance adjustment, an eight week follow-up period was arranged that allowed for habituation and, if necessary, adjustment of CPAP or the oral appliance. After this period, a second polysomnographic study was performed. If polysomnography indicated an AHI ≥5, CPAP or the oral appliance was further adjusted by the physician (not during polysomnography). A third polysomnographic study was performed 4 weeks after that adjustment. Treatment was considered successful when the AHI either was <5 or showed "substantial reduction," (23) defined as a reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no OSAS symptoms (6) while using therapy. Patients for whom oral appliance or CPAP therapy was successful continued this treatment. If one of both treatments was not

successful at any time during the follow-up period, patients were offered the alternative therapy (CPAP or oral appliance, respectively), which was titrated as described above. After a two-year follow-up period all patients were subjected to a final polysomnographic evaluation. Patients were always encouraged to contact our clinic between regular follow-up appointments when problems were faced concerning the oral appliance, CPAP device, or treatment effect.

Study model analysis

At baseline and after two years of treatment, dental plaster study models in full occlusion, based on alginate impressions of the upper and lower dental arches, were obtained from all patients to determine clinically relevant variables related to the patient's occlusion (16, 21, 25). The intermaxillary relationship between the upper and lower arch was recorded with the vinyl polysiloxan registration material Exabite II NDS™ (GC America Inc, Alsip, Il, USA) in maximal occlusion. Models were also placed and rimmed into maximal occlusion in order to perform measurements with a digital sliding calliper with a 0.01 mm resolution (26). All measurements were carried out on models in full occlusion, mounted in an articulator (Artex®, Girrlach Dental, Koblach, Germany) with a bilateral sagittal condylar inclination of 32.5 degrees and Bennett-angle of 17.5 degrees. The degree of mandibular protrusion and mouth opening, associated with wearing an oral appliance, was also measured with a digital sliding calliper while the oral appliance was fixed on the models in the therapeutic position, which were subsequently mounted in the articulator. Measurements were performed twice by one observer (K.F.) who was blinded for the patient's treatment. For continuous variables the mean of both measurements was used for further analysis.

Anterior overjet and overbite were calculated as the mean of the overjet or overbite measured at both maxillary central incisors. Anterior overjet was defined as the horizontal distance from the mesial end of the incisal edge of the upper central incisor to the labial plane of the lower central incisor. Anterior overbite was defined as the vertical distance of the incisal edge of the lower central incisor to the horizontal projection of the incisal edge of the upper central incisor on the labial plane of the lower central incisor. The difference (baseline versus follow-up) in anterior-posterior relationship was measured at the buccal sites of the first molars. In order to obtain reproducible measurements, the position of the buccal groove of the mandibular first molar was marked on the buccal site of the maxillary antagonist. Negative values are related to a mesial shift of the dentition in the mandible and positive values are related to a distal shift of the dentition in the mandible. If the first permanent molars were missing, the second permanent molars were used for measurements.

Angle's classification system (27) of malocclusion was used to identify the anterior-posterior relationship of the upper and lower first molars and upper and lower cuspids and was classified as Class I (neutrocclusion), Class II (distocclusion) and Class III (mesiocclusion). Angle classifications were determined at baseline and follow-up for the left and right molar-occlusion (if the upper and lower first molars were present; Table 2) and for the left and right cuspid-occlusion (if the upper and lower cuspid were present; Table 3). When models were missing, damaged or if too many teeth were missing for adequate classification, the patient was listed as *indefinable*.

Table 2. Molar occlusion at baseline and follow-up review.

Angle's classification	Oral appliance group (n=29)				CPAP group (n=34)			
	Molar occlusion right side		Molar occlusion left side		Molar occlusion right side		Molar occlusion left side	
	baseline	follow-up	baseline	follow-up	baseline	follow-up	baseline	follow -up
Class I	n=7	Unchanged (n=4) Class III (3)	n=6	Unchanged (n=4) Class II (n=1) Indefinable (n=1)	n=9	Unchanged (n=7) Class II (n=1) Indefinable (n=1)	n=6	Unchanged (n=4) Class II (n=1) Indefinable (n=1)
Class II	n=14	Unchanged (13) Class III (n=1)	n=14	Unchanged (n=11) Class I (n=2) Class III (n=1)	n=16	Unchanged (n=15) Class I (n=1)	n=15	Unchanged (n=14) Indefinable (n=1)
Class III	n=0		n=1	Unchanged (n=1)	n=4	Unchanged(n=3) Class I (n=1)	n=4	Unchanged (n=2) Class I (n=2)
Indefinable	n=8		n=8		n=5		n=9	

Abbreviations: CPAP= Continuous Positive Airway Pressure.

Table 3. Cuspid occlusion at baseline and follow-up review.

Angle's classification	Oral appliance group (n=29)				CPAP group (n=34)			
	Cuspid occlusion right side		Cuspid occlusion left side		Cuspid occlusion right side		Cuspid occlusion left side	
	baseline	follow-up	baseline	follow-up	baseline	follow -up	baseline	follow-up
Class I	n=9	Unchanged (n=5) Class III (4)	n=9	Unchanged (n=4) Class III (n=5)	n=13	Unchanged (n=12) Class II (n=1)	n=8	Unchanged (n=4) Class I (n=1) Indefinable (n=3)
Class II	n=18	Unchanged (16) Class III (n=2)	n=18	Unchanged (n=15) Class I (n=3)	n=19	Unchanged (n=16) Class I (n=2) Class III (n=1)	n=24	Unchanged (n=22) Class I (n=1) Indefinable (n=1)
Class III	n=1	Unchanged (n=1)	n=2	Unchanged (n=2)	n=1	Unchanged (n=1)	n=2	Unchanged (n=2)
Indefinable	n=1				n=1			

Abbreviations: CPAP= Continuous Positive Airway Pressure.

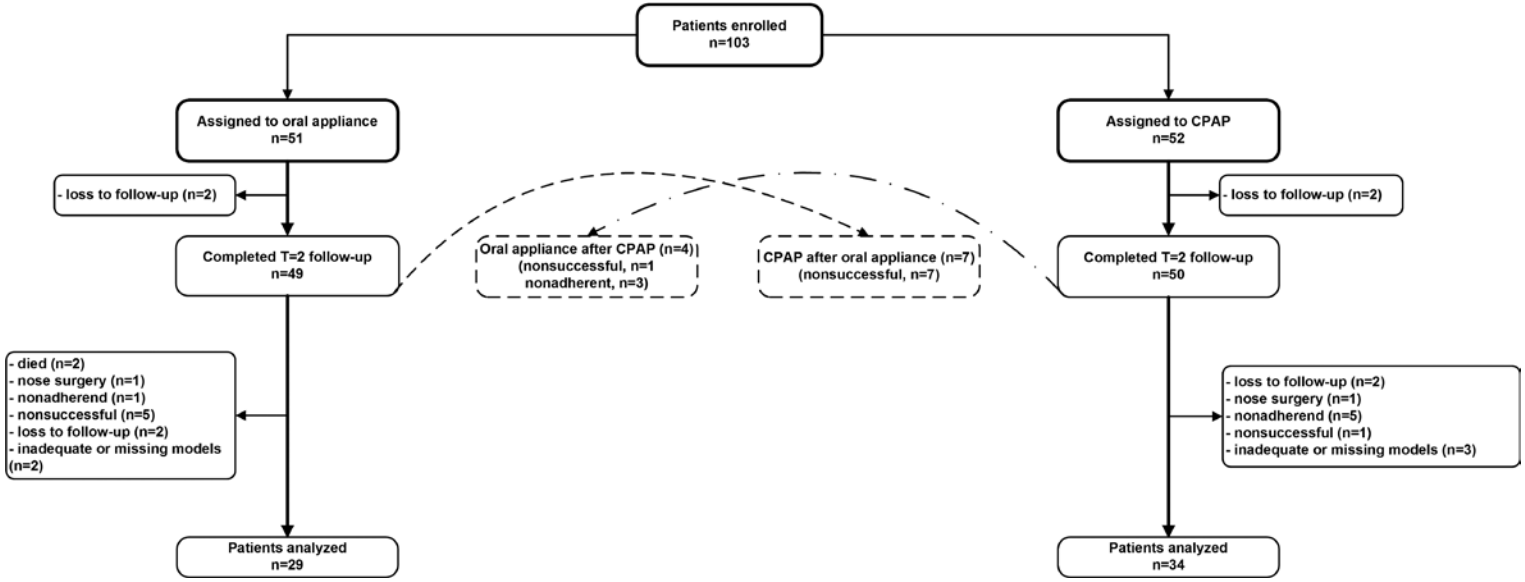

Figure 1. Flow diagram of the patient selection procedure.
Patients who discontinued treatment for any reason were considered nonadherent to treatment. Treatment was considered successful when the apnoea-hypopnoea index was <5 or showed substantial reduction in the index of at least 50% from the baseline value to a value of <20 in a patient without subjective OSAS symptoms (6) while using therapy. Patients not meeting these criteria were considered nonsuccessful.

Occlusal contact points (relationship between maxillary and mandibular teeth in maximal occlusion) were made visible using articulation paper directly on the models. Biting forces were not applied in a standardized way as we did not have the disposal of such equipment. Subsequently the number of teeth in contact was determined, not the size of the contact points. The number of occlusal contact points was determined for the (pre)molar region and for the cuspid-incisor region of the maxillary model.

The left and right transversal relation between the maxillary and mandibular teeth in the (pre) molar region was determined as normal, end-to-end or cross bite. If the transversal relation of one or more teeth at the (pre)molar region changed after the follow-up period, this was recorded.

Crowding was defined (visually) as an altered tooth position as a result of inadequate space in the alveolar arch and was scored as increased, decreased or no change after the follow-up period. Evaluation of interproximal spaces (diastemas) was done at baseline and after follow-up for both arches and was classified as unchanged, increased or decreased. Interproximal spaces at follow-up that were the result of tooth extractions during the follow-up period were not counted.

Dummies incorporated in fixed bridges were included in all analyses but were not counted as present permanent teeth.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). All variables were normally distributed and their means and standard deviations (s.d.) are reported. The AHI of the oral appliance- and CPAP patients at baseline was distributed normally after logarithmic transformation. To compare outcomes between continuous variables at baseline and follow-up, paired Student's t-tests were performed. For comparing outcomes for continuous variables between the oral appliance and CPAP group, unpaired Student's t-tests were performed. For comparing categorical variables within and between both treatment groups, the Fischer's exact test was applied. Linear regression analysis was used to determine the relationship between possible dental side-effects and other therapy- or patient-related variables during the follow-up period (e.g. mandibular protrusion, degree of OJ and OB). Regression coefficients (β) and their 95% Confidence Intervals (CI) are reported. Other analyses were exploratory. A significance level of 0.05 was predefined in all cases.

Results

For analysis, 29 and 34 patients were included in the oral appliance group and the CPAP group respectively, after two years of treatment (Fig. 1). The mean follow-up period was 2.3 (± 0.2) years in the oral-appliance group (range 2.1-3.1 years) and 2.4 (± 0.3) years in the CPAP group (range 2.1-3.2 years). The mean mandibular protrusion during the follow-up period was 79 (± 19) % of the patient's maximum protrusion. The numbers of nights and hours per night that both therapies were used did not significantly differ between both treatment groups (Table 1).

Study model analysis

Regarding baseline characteristics of the patients included in the analysis, (Table 1), no significant differences were found between the oral appliance- and CPAP group.

A significant decrease in overbite (-1.2 ± 1.1 mm; ($p<0.00$)) and overjet (-1.5 ± 1.5 mm; ($p<0.00$)) was found in the oral appliance group compared to the CPAP group as well as a significantly ($p<0.00$) larger anterior-posterior change in occlusion (-1.3 ± 1.5 mm) compared to the CPAP group (-0.1 ± 0.6 mm) (Table 1). For the oral appliance group, linear regression analysis revealed a significant association between the change in overbite and the amount of mandibular protrusion (β=-0.02, 95% CI (-0.04 to 0.00)). We did not find a significant association between the baseline OJ or OB and the change in OJ or OB after long-term oral appliance- or CPAP use.

When evaluating the number of occlusal contact points between the upper- and lower dental arch in the cuspid-incisor region, there was no tendency towards the occurrence of an open bite in the frontal region in either the oral appliance- or CPAP group. We found a significant decrease in the number of occlusal contact points in the (pre)molar region in both the oral appliance- ($p<0.00$) and CPAP group ($p=0.03$) after two years of treatment (Table 1).

Transversal relation of the teeth in the (pre)molar region did change in 8 patients in the oral appliance group and in 2 patients in the CPAP group after two years of treatment. In 4 patients from the oral appliance group, the bilateral transversal relation changed from normal to end-to-end and in 1 patient only the right side transversal relation changed from normal to end-to-end. In 1 patient a bilateral cross bite changed to a complete reversed transversal relation (maxillary inner bite). However, this patient was familiar with a mid-face hypoplasia and a class III malocclusion before starting oral appliance therapy. Furthermore, in 4 patients the bilateral transversal relation changed from end-to-end to a bilateral cross bite. In the CPAP group one patients' bilateral transversal relation changed from normal to a bilateral cross bite and one changed from a normal bilateral transversal relation to a bilateral end-to-end relation.

For the CPAP group, left side molar occlusion could be assessed at baseline in 25 patients and right side molar occlusion in 29 patients (Table 2). After two years of treatment, a change in right side molar occlusion was observed in 3 patients (10%) and in the left side molar occlusion also in 3 patients (12%). Furthermore, left side cuspid occlusion was determined in all 34 patients and right side cuspid occlusion for 33 patients (Table 3). After two years of treatment, a change in right side cuspid occlusion was verified in 4 patients (12%) and in 1 patient (3%) for the left side cuspid occlusion.

For the oral appliance group, both left and right side molar occlusion could be determined at baseline in 21 patients (Table 2). After two years of treatment, a change in right side molar occlusion was observed in 4 patients (20%) and in the left side molar occlusion also in 4 patients (20%). Furthermore, left side cuspid occlusion was assessed for all 29 patients and right side cuspid occlusion for 28 patients (Table 3). After two years of treatment, a change in right side cuspid occlusion was observed in 6 patients (21%) and in 8 patients (28%) for the left side cuspid occlusion.

No significant differences in crowding were observed after two years of treatment for both treatment groups. In the oral appliance group no differences were found in crowding for the upper

dental arch while one patient showed less crowding for the lower dental arch. In the CPAP group one patient showed less crowding for the upper dental arch, one showed less crowding and one more crowding for the lower dental arch.

No significant differences in interproximal spaces were found for the upper and lower arch between the oral appliance- and the CPAP group. In the oral appliance group, an increase in interproximal spaces in the upper dental arch was found in 2 patients and a decrease in 2 patients. For the lower dental arch, an increase in interproximal spaces was found in 7 patients. In the CPAP group, an increase in interproximal open spaces of the upper dental arch was found in 1 patient whereas for the lower dental arch, interproximal spaces were increased in 4 patients.

Discussion

To our knowledge, this is the first study in which changes in dental morphology as a result of long-term oral appliance therapy are evaluated in a controlled study concerning mild-to-severe OSAS patients. Oral appliance therapy is generally considered a life-long treatment modality. This study demonstrated that a decrease in overjet, overbite, number of occlusal contact points and a different anterior-posterior relationship are dental changes most likely to occur. Furthermore, we found an association between the decrease in overbite and the amount of mandibular protrusion associated with wearing an oral appliance. Moreover, there was a tendency towards a mesiocclusion after two years of oral appliance therapy compared to CPAP therapy. In the oral appliance group we also found a tendency towards the development of a (bi)lateral crossbite in the (pre) molar region. In the oral appliance group, more patients had a shift in molar- and cuspid occlusion from class I to class III or a shift from class II to class I or III compared to the CPAP group.

Changes in overbite, overjet and anterior-posterior relationship of the occlusion as a result of long-term oral appliance therapy have also been described in previous studies (16, 18, 19, 21, 28). It is generally hypothesized that these changes can be attributed to a labially directed force to the mandibular incisors and a palatally directed force to the maxillary incisors during oral appliance therapy while the mandible attempts to return to a more dorsal position. However, in a study of Ringqvist and co-workers (12), no significant changes in overjet and overbite were found after 2 years of oral appliance therapy. This may be explained by differences in appliance design. The oral appliance used in our study was made of hard acrylate which covers the entire upper and lower dental arch, while, in the appliance that was used by Ringqvist and co-workers both frontal parts were not covered by acrylate, possibly resulting in less forces applied to the upper and lower incisors. This can be a possible explanation for the absence of significant changes in overjet and overbite. In a study by Ghazal and co-workers, a significant decrease in overbite but not overjet was found (25). The appliance used in that study was a Thornton Adjustable Positioner (TAP) like the one used in this study. However, in the latter mentioned studies, only patients with mild and moderate OSAS patients were included (12, 25). In this study, patients with mild, moderate and severe OSAS were included and protrusive positions of the mandible over 75% were applied in some patients. The relationship between the amount of mandibular protrusion and efficacy of an oral appliance has previously been described (29, 30). Therefore, a second explanation for the

different findings regarding changes of the overjet and overbite could be that an oral appliance is already effective in a less protrusive position in mild and moderate OSAS patients, resulting in less severe dental side-effects.

Regression analysis showed that there appears to be an association between the decrease in overbite and the extent of mandibular protrusion. This result confirms the finding of a previous cephalometric study conducted in the same patient population (11). Both separate findings suggest that it is important to coach patients which are treated with an oral appliance, as with an adjustable appliance, there is a risk that patients advance the mandible beyond the optimal protrusive position.

Like in several other studies (16, 21, 22) we found a significant decrease in the number of occlusal contact points in the (pre)molar region in both the oral appliance group and CPAP group. As long-term oral appliance use results in a decrease in overjet and overbite it is conceivable that, because of the incisal guidance phenomenon, the bite tends to open in the (pre)molar region, resulting in a decrease in the number of occlusal contact points in the (pre)molar region. Martinez-Gomis and co-workers (31) also found a significant reduction in posterior occlusal contact points after 2 years of oral appliance use. This tendency, however, reversed during the period of 2-5 years of treatment. The reason for this phenomenon can be the development of a new occlusal equilibrium overtime. Therefore, it seems viable that these dental changes tend to stabilize over time. In this study, we also found a decrease in the number of occlusal contact points in the CPAP group. It has recently been advocated that nasal CPAP may change craniofacial form and may alter the relationship between the dental arches (32). A retroclination of the maxillary incisors after long-term nasal CPAP use has also been reported in the latter study. As nasal CPAP is administered through a tight fitted (nose)-mask, it could be hypothesized that the pressure of this mask results in palatally directed forces on the frontal part of the upper dental arch. The same incisal guidance phenomenon as mentioned before could therefore explain the decrease in number of occlusal contact points in our CPAP patients. Nevertheless, none of the patients using CPAP in our study did report any changes in occlusion. In a study, published by Ueda and co-workers (33), it was suggested that in patients using an oral appliance, certain jaw exercises might help to relieve stiffness of the masticatory muscles and accelerate the repositioning of the mandible to the normal position after a night of oral appliance use. It furthermore may inhibit or minimize the occlusal functional changes in predisposed patients. These results may indicate the importance of such additional exercises in patients using an oral appliance that are prone to occlusal changes.

The results presented in table 2 and 3 suggest that there is a tendency towards a mesial shift of the molar- and cuspid-occlusion after long-term use of an oral appliance. This result is in agreement with previously reported findings (16, 19-21). However, as proposed by Almeida and co-workers (21), not all occlusal changes, which could be the result of long-term oral appliance therapy, should be interpreted as unfavourable. Regarding the patients in this study, favourable changes were more likely to be class II and the unfavourable changes seem to occur more in patients with class I baseline occlusion. We furthermore found a tendency towards the development of (bi)lateral crossbites in the (pre)molar region after long-term oral appliance use. This could be

explained by the fact that, with a mesial shift in occlusion, the broader part of the mandibular dental arch will occlude with the narrower part of the maxillary dental arch. These results reinforce the importance of good pre-therapeutic information to our patients, especially in patients in whom larger occlusal changes are to be expected.

In conclusion we found that long-term oral appliance therapy and CPAP may result in dental changes in OSAS patients. However, when treating a serious and sometimes life threatening disorder as OSAS, therapeutic efficacy should supersede the maintenance of a patients' baseline craniofacial morphology. Discontinuation of oral appliance therapy because of the development of dental side-effects should only be considered in patients who are able to tolerate or accept another effective treatment modality for their OSAS. Regarding possible dental side-effects that may occur, we would like to emphasize the importance of providing adequate information to the patients before commencing oral appliance therapy. At least it should be mentioned that there is a chance that the overjet and overbite will decrease which can result in a suboptimal occlusion (e.g. less occlusal contact points and a possible development of (bi)lateral crossbite in the (pre) molar region) and altered aesthetics.

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CHAPTER 4.3

Long-term oral appliance therapy in obstructive sleep apnoea syndrome; a controlled study on temporomandibular side-effects

This chapter is an edited version of:

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Abstract

The objective of this study was to assess variations in the occurrence of temporomandibular disorders (TMDs) and the risk of developing pain and function impairment of the temporomandibular complex in obstructive sleep apnoea syndrome (OSAS) patients treated with either an oral appliance or continuous positive airway pressure (CPAP) in a two-year follow-up study. In addition we assessed the relationship between the mean mandibular protrusion, and the frequency of wearing the appliance during follow-up with the occurrence of pain and function impairment of the temporomandibular complex.

Fifty-one patients were randomized to oral appliance therapy and fifty-two patients to CPAP therapy. TMDs (diagnosed according to the Axis I Research Diagnostic Criteria for TMD), pain intensity and disability, and mandibular function impairment were recorded at baseline, after 2 months, 1 year and 2 years of therapy.

Only in the initial period of treatment, the occurrence of pain-related TMDs was considerably higher (24%) in the oral appliance group compared to CPAP (6%). Oral appliance therapy furthermore resulted in more temporomandibular pain compared to CPAP (Odds ratio [OR] 2.33, 95% Confidence Interval [CI] (1.22–4.43)). However, there were no limitations in mandibular function in both groups during the (entire) follow-up period.

Although generally not serious and of transient nature, oral appliance therapy results in more pain related TMDs in the initial period of use compared with CPAP therapy. Because of the transient nature, this pain is not a reason to contra-indicate an oral appliance in OSAS patients. Moreover, TMDs and the risk of developing pain and function impairment of the temporomandibular complex appear limited with long-term oral appliance use.

Introduction

Obstructive sleep apnoea syndrome (OSAS) is a highly prevalent sleep-related breathing disorder affecting approximately 4% of the male and 2% of the female adults in the North-American population (1). The disorder is characterized by disruptive snoring and repetitive partial or complete obstructions of the upper airway (i.e. hypopnoeas and apnoeas, respectively) during sleep (2). This disrupted sleep may result in various (serious) neurobehavioral and cardiovascular sequelae, ultimately depriving the patient's quality of life and life expectancy (3, 4). Standard treatment with Continuous Positive Airway Pressure (CPAP) is very effective in reducing symptoms (5, 6). However, because of the obtrusive nature of CPAP, patients may abandon or adhere poorly to this therapy (7). Oral appliance therapy has been demonstrated an effective alternative in treating OSAS, especially in the mild and moderate spectrum of the disorder and in patients unwilling or unable to tolerate CPAP (8). Oral appliances generally aim at relieving the upper airway obstructions by positioning the mandible in a forward and downward position (9).

Mild and 'transient' side effects are commonly reported in the initial period of oral appliance use (10-13). Known side effects, associated with long-term use of an oral appliance are predominantly dental in nature and include a decreased overjet and overbite (14-16). Furthermore, a change in inclination of the mandibular and maxillary incisors has been reported (14-16). Moreover, some authors have reported a downward and forward displacement of the mandible as a result of oral appliance therapy (15, 17, 18).

Temporomandibular disorders (TMDs), is a collective term that embraces a number of clinical problems that involve the masticatory muscles, the temporomandibular joint, and the associated structures (19). When using an oral appliance during sleep, the mandible is positioned in an unnatural forward and downward position, which could ultimately result in TMDs. Studies regarding TMDs associated with oral appliance therapy for the management of OSAS are still limited in number and quality (20-25). Most studies to date have been retrospective, comprised small study samples or did not include a (matched) control group. Furthermore, in most studies the oral appliance was not adjustable but fixated the patients' mandible in a predefined protrusive position (50-75% of the maximal mandibular protrusion). Therefore, a clear association between the mandibular protrusion and the occurrence of TMDs is still unknown. It could be hypothesized that more serious TMD-related complaints will occur in patients with the mandible positioned in a more forward position or in patients using the oral appliance more frequently.

The objectives of this parallel randomized controlled study were to assess:

1. Variations in the occurrence of TMDs and the risk of developing pain and function impairment of the temporomandibular complex in OSAS patients treated with an oral appliance compared with CPAP during a two-year follow-up.
2. The relationship between the mean mandibular protrusion, and the frequency of wearing the appliance during follow-up with the occurrence of pain and function impairment of the temporomandibular complex.

Table 1: Baseline characteristics of 103 patients treated with an oral appliance or CPAP.

Variable	Oral Appliance * (n=51)	CPAP* (n=52)
Male / female ratio	43 / 8	49/3
Age (years)	49 ± 10	49 ± 10
Body-mass index (kg/m^2)	32 ± 6	33 ± 6
Apnoea-hypopnoea index (no/hour)	39 ± 31	40 ± 28
Neck circumference (cm)	44 ± 4	45 ± 4
minSaO_2 (%)	78 ± 9	78 ± 10
OSAS severity	Non-severe: n=25 (49%) Severe: n=26 (51%)	Non-severe: n=25 (48%) Severe: n=27 (52%)

* values are means ± standard deviations.
Abbreviations: minSaO2 = lowest oxyhemoglobin saturation during sleep.

Materials & Methods

Patient Selection

The effectiveness of an oral appliance in the treatment of OSAS, compared with CPAP, has been evaluated in a previous executed randomized controlled trial (26). The materials and methods of this specific study are briefly summarized below. All patients were recruited through the Department of Home Mechanical Ventilation of the University Medical Center Groningen, the Netherlands. Subjects over 20 years of age and diagnosed with OSAS (apnoea-hypopnoea index (AHI) ≥ 5) based on polysomnography (27) were eligible. If patients fulfilled predefined medical, psychological, and dental inclusion criteria, they were selected for the study (26) and subsequently randomized for either oral appliance- (n = 51) or CPAP therapy (n = 52).

For the present study, we assessed the occurrence of disorders of the temporomandibular complex as a result of long-term use of an oral appliance compared to CPAP in OSAS patients (Table 1). Patients considered nonsuccessful or nonadherent (26) were offered to switch to the alternative therapy at any time during the follow-up. Details of patient selection criteria for our study are provided in figure 1.

The present study was approved by the Groningen University Medical Center's Ethics Committee. Written informed consent was obtained from each patient before enrolment.

Variables

At baseline clinical variables were determined (26). Prior to (T0), after two months (T2), one year (T15) and two years (T27) of therapy, the occurrence of TMDs was assessed based on Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) Axis I (Table 3) (28). The RDC/TMD is developed for research purposes and constitutes a reliable system for the assessment of

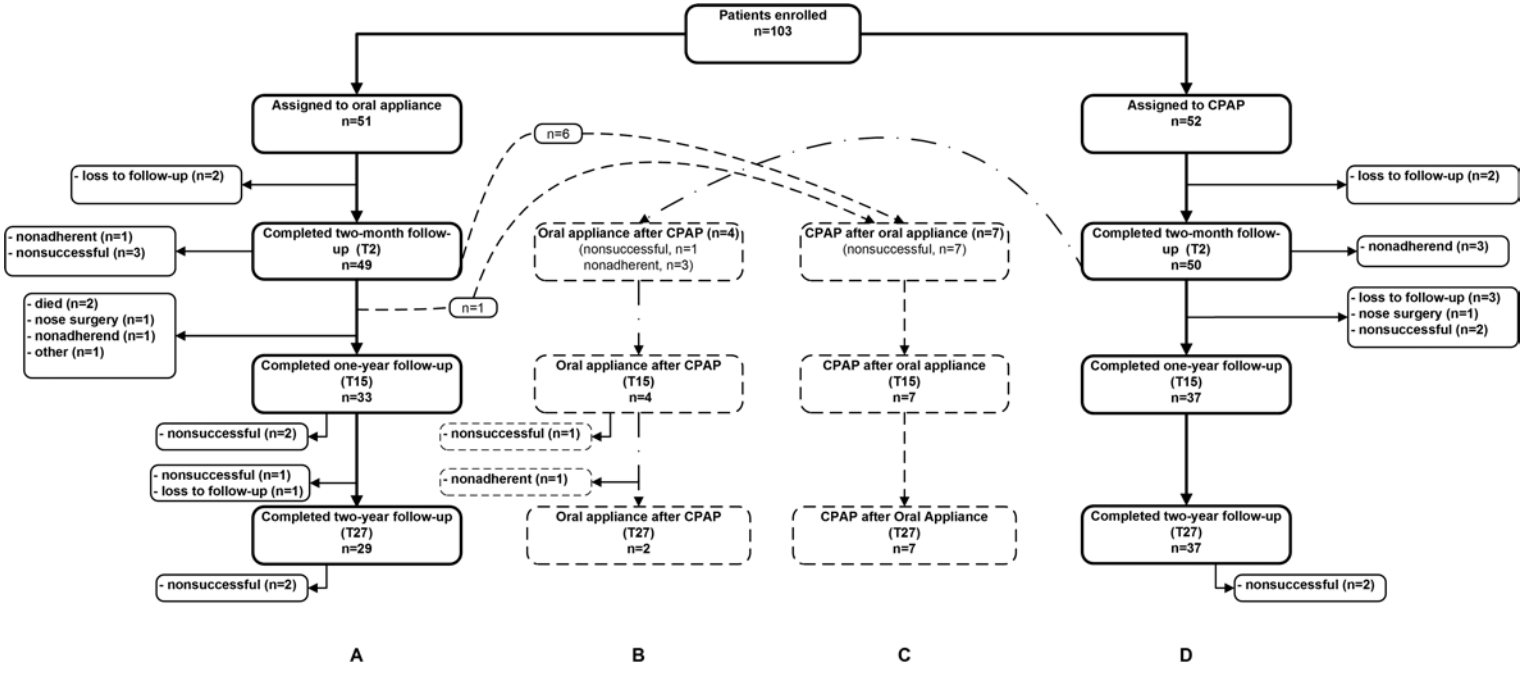

Figure 1. Flow diagram of the patient selection procedure.

Patients who discontinued treatment for any reason were considered *nonadherent* to treatment. Treatment was considered successful when the apnoea-hypopnoea index was < 5 or showed substantial reduction, defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient without subjective OSAS symptoms (27) while using therapy. Patients not meeting these criteria were considered *nonsuccessful*.

Table 2: Classification of the outcome of the seven-item questionnaire for graded chronic pain; Research Diagnositic Criteria for Temporomandibular Disorders (RDC/TMD): Axis II.

Grade	Description
Grade 0	No temporomandibular pain in the prior 6 months
Grade I	Low disability – Low intensity pain
Grade II	Low disability – High intensity pain
Grade III	High disability – Moderately limiting
Grade IV	High disability – Severely limiting

Dworkin and LeResche [28].

TMDs (28, 29). Axis I from the RDC/TMD is based on clinical signs and symptoms. The RDC/TMD Axis II was designed to grade chronic pain severity (Graded Chronic Pain Scale). Examinations were standardized and two experienced observer (MD, AH) were responsible for all examinations throughout the study. The observers reviewed the RDC/TMD procedure after being thoroughly instructed by an orofacial pain specialist (BS). According to the RDC/TMD guidelines, clinical diagnoses were made (Table 3). For this study, the patient rather than the joint was the entity of research. In theory, each patient can have multiple RDC diagnoses (maximum of 5). In practice, patients with more than 3 RDC diagnoses are very rare (28).

To assess pain of the temporomandibular complex, the RDC/TMD Axis II was used. This scale has been specifically designed to grade chronic pain severity, ranging from grade 0 to grade IV (Table 2) (28). At all time-points (T0, T2, T15 and T27) patients filled out the seven-item Graded Chronic Pain Scale. Two clinical cut-off points were defined, i.e. grade > 0 represents 'pain' and grade > II represents 'pain induced limitation'.

At all time-points (T0, T2, T15 and T27), the Mandibular Function and Impairment Questionnaire (MFIQ) was filled out by all patients to subjectively assess function impairment of the temporomandibular complex during therapy. The MFIQ is a validated questionnaire to assess the impact of TMDs on mandibular function and movements in patient's daily life circumstances (30). This questionnaire scores perceived difficulty of 17 representative mandibular functions in relation to joint or muscle complaints. The possible answers are scored on a five-point Likert scale from 0-4, representing "no difficulty (0)" to "very great difficulty or impossible without help (4)". The sum item score for function impairment ranges from 0-68. Then the raw component score was calculated (range 0-1). From this raw component score the Function Impairment Rating Scale (FIRS) (range 0-5) was determined and thereupon, to enhance interpretation, the FIRS was converted to a more qualitative indication of the level of function impairment (low (FIRS 0 or 1)/ moderate (FIRS 2 or 3)/ severe (FIRS 4 or 5)) (30). Finally, at each time-point, patients filled out a questionnaire about therapy use. In this questionnaire patients were asked how many nights per week and how many hours per night therapy was used.

Table 3: Number of patients diagnosed with Temporomandibular Disorders (TMDs) according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD): Axis I at each checkup.

Clinical diagnosis* (RDC/TMD)	T0			T2			T15			T27		
	CPAP (n=52)	OA (n=51)	total (n=103)	CPAP (n=50)	OA (n=49)	total (n=99)	CPAP (n=41)	OA (n=40)	total (n=81)	CPAP (n=39)	OA (n=36)	Total (n=75)
No TMD	40	33	73	36	27	63	32	27	59	31	24	55
1a:myofascial pain‡	*0*	*1*	*1*	*1*	*2*	*3*	*0*	*1*	*1*	*0*	*1*	*1*
2a: disc displacement with reduction	7	14	21	9	10	19	3	10	13	3	10	13
2b: disc displacement without reduction with limited opening	0	0	0	0	0	0	0	0	0	0	1	1
3a: Arthralgia	*1*	*1*	*2*	*1*	*4*	*5*	*2*	*1*	*3*	*1*	*0*	*1*
3c: Osteoarthrosis of the temporomandibular joint	2	0	2	*2*	0	2	2	0	2	2	0	2
1a + 2a	*0*	*1*	*1*	*0*	*2*	*2*	*0*	*0*	*0*	*0*	*0*	*0*
1a + 3a	*1*	*1*	*2*	*1*	*2*	*3*	*1*	*1*	*2*	***2***	*0*	*2*
2a + 3a	*0*	*0*	*0*	*0*	*2*	*2*	*1*	*0*	*1*	*0*	*0*	*0*
2a +3c	1	0	1	0	0	0	0	0	0	0	0	0
Total TMD (%)	23	35	29	28(↑5)†	45 (↑10)	36 (↑7)	22 (↓6)	32 (↓13)	27 (↓9)	21 (↓1)	33 (↑1)	27
Pain related TMD (%)	4	8	6	6 (↑2)	24 (↑16)	15 (↑9)	10(↑4)	8 (↓16)	9 (↓6)	8 (↓2)	3 (↓5)	5 (↓4)

* Only those clinical diagnoses or combinations of diagnoses which were prevalent during the study.

† Within parenthesis the percentage increase (↑) or decrease (↓) in the occurrence of TMD compared to the preceding check-up is described.

‡ Diagnoses or combinations of diagnoses in Italic represent pain related diagnoses.

Interventions

The oral appliance used in this study (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a forward and downward position. This type of oral appliance is often referred to as a Mandibular Advancement Device (MAD). By turning a propulsion screw that was incorporated anteriorly in the appliance, patients could adjust the mandibular advancement with 0.2 mm increments with each turn. The maximum range of mandibular protrusion was first determined with a George-Gauge™ (H-Orthodontics, Michigan City, IN, USA). When initiating oral appliance therapy, the mandible was set at approximately 50% of the patient's maximum protrusion. After having accustomed to this protrusive position during a two-week period, patients were allowed to further adjust the oral appliance during a 6-week period. When subjective OSAS symptomatology appeared to persist, patients were instructed to advance the mandible each night with 1 to 2 increments (i.e. 0.2-0.4 mm). This "titration" of the oral appliance was continued until subjective OSAS symptoms (27) were adequately improved or until further protrusion of the mandible resulted in discomfort. The mean mandibular protrusion during the follow-up period (expressed as percentage of the maximum mandibular protrusion) was used for further analysis. The vertical dimension of the oral appliance was kept constant during the entire follow-up period. Both mandibular protrusion and mouth opening (including the vertical overbite) imposed by the oral appliance were measured with a digital sliding calliper. These measurements were carried out at baseline, after two months, one year and two years of treatment. At these time-points also other clinical measurements (weight, length, neck circumference and intoxications) were carried out.

CPAP-titration was performed during an afternoon nap. This technique, aimed at abolishing all signs of apnoeas, hypopnoeas and snoring, has been shown to be an appropriate procedure for the effective titration of CPAP (31).

Following CPAP- and oral appliance adjustment, an eight week follow-up period was arranged that allowed for habituation and, if necessary, adjustment of CPAP or the oral appliance. After this period, a second polysomnographic study was performed. If polysomnography indicated an apnoea-hypopnoea index ≥5, CPAP or the oral appliance was further adjusted by the physician (not during polysomnography). A third polysomnographic study was performed 4 weeks after that adjustment.

Treatment was considered effective when the apnoea-hypopnoea index either was <5 or showed "substantial reduction," (26) defined as a reduction in the index of at least 50% from the baseline value to a value of <20 in a patient who had no OSAS-symptoms while using therapy. Patients for whom oral appliance or CPAP therapy was effective continued this treatment. If one of both treatments was not effective at any time during the follow-up period, patients were offered the alternative therapy (CPAP or oral appliance, respectively), which was titrated as described above. After a two-year follow-up period all patients were subjected to a final polysomnographic evaluation. Patients were always encouraged to contact our clinic between regular follow-up appointments when problems were faced concerning the oral appliance, CPAP device or treatment effect.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). All continuous demographic variables at baseline were normally distributed and their means and standard deviations (s.d.) are reported. The AHI of the oral appliance and CPAP patients at baseline was normally distributed after logarithmic transformation.

An "intention-to-treat" analysis (Fig. 1: group A+C versus group B+D) was carried out for all measurements (i.e., all patients were analyzed in the group to which they were randomized, regardless of whether they complied with the assigned treatment). Statistical analysis for longitudinally, repeated measurements were performed using Stata (version 10.1, StataCorp, College Station, TX, USA) by means of Generalized Estimating Equations (GEE). With GEE the joint relationship of different variables (e.g. difference in pain, pain induced limitations and the MFIQ score) at different time-points is analyzed.

For oral appliance therapy, the mean mandibular protrusion during the follow-up, therapy use or possible switching of therapy were related to the MFIQ scores or pain in the temporomandibular complex with GEE models. Odds ratios (OR) for dichotomous variables and regression coefficients (β) for continuous variables and their 95% confidence intervals (CI's) are reported. The significance level α of all analyses was set at 5%. The occurrence of TMDs at different time-points is reported in a descriptive way.

Results

After two years, 36 out of 51 patients randomized to an oral appliance (71%) and 39 out of 52 patients randomized to CPAP (75%) completed the follow-up. In the oral appliance group, 29 patients (57%) completed the 2-year follow-up still using their oral appliance, while in the CPAP group, 37 patients (71%) completed the 2-year follow-up using CPAP. Eleven patients switched to the alternative therapy during the follow-up (Fig. 1: group B and group C). Seven patients switched from oral appliance therapy to CPAP therapy (all considered nonsuccessful). Four patients switched from CPAP therapy to oral appliance therapy (1 was considered nonsuccessful and 3 nonadherent), of whom 2 completed the 2-year follow-up (Fig. 1: group B).

In the oral appliance group (n=36), the mean (± s.d.) mandibular protrusion during the follow-up period was 76 (± 25) % of the maximum mandibular protrusion. The mean mouth opening (including overbite) while wearing the oral appliance was 12.8 (± 2.7) mm. Patients in the oral appliance group used their device on average 6.7 (± 0.6) nights per week and 7.2 (± 0.8) hours per night. In the CPAP group (n=39) patients used their device on average 6.9 (± 0.4) nights per week and 6.9 (± 1.3) hours per night. No patient withdrew from the study during the follow-up period because of signs or symptoms of TMDs.

Clinical measurements

The outcomes of the RDC/TMD indicate that most of the patients in both the oral appliance

and CPAP group could be classified as 'no-TMD' at all time-points (Table 3). At baseline, 12 out of 52 patients (23%) in the CPAP group and 18 out of 51 patients (35%) in the oral appliance group were diagnosed with TMDs, of which a disc displacement with reduction (2a) was the most prevalent in both groups. In the oral appliance group, however, this diagnosis was twice as prevalent when compared with the CPAP-group. Two patients in the CPAP-group were diagnosed with osteoarthrosis (3c) at baseline, whereas this condition was not observed in the oral appliance group. After two months of therapy (T2), there was an increase in occurrence of 5% and 10% of total TMDs compared to baseline in the CPAP- and oral appliance group, respectively. At the one-year follow-up (T15) a decrease in the occurrence of TMDs was observed in both CPAP (7%) and oral appliance group (12%) when compared with the 2-month follow-up. Compared to the one-year follow-up, only small changes in the occurrence of TMDs occurred after two years (T27) of treatment in both groups (1%).

At baseline (T0), 2 out of 52 patients (4%) in the CPAP-group and 4 out of 51 patients (8%) in the oral appliance group were diagnosed with either one or a combination of pain-related diagnoses (i.e. tendomyalgia (1a), arthralgia (3a) and osteoarthritis (3b)). After 2 months, an increase in occurrence of 2% and 16% of one or a combination of pain-related TMDs was observed in the CPAP- and oral appliance group, respectively. At the one-year follow-up, there was an increase in the occurrence of pain-related TMDs in the CPAP group (4%), while in the oral appliance group a decrease (16%) was observed when compared with the 2-month follow-up. Compared to the one-year follow-up, only small changes in the occurrence of pain-related TMDs occurred after two years (T27) of treatment in both groups.

Questionnaires

A significant difference was found in pain intensity between oral appliance and CPAP therapy at different time-points. Patients receiving oral appliance therapy have a higher risk of developing pain than patients using CPAP therapy during a two-year follow-up (OR=2.33, 95% CI (1.22–4.43)). No associations were found between pain intensity and mandibular protrusion (OR=1.02 (0.84–1.24)), therapy use (OR=1.13 (0.90–1.44)) or switching of therapy (OR=0.87 (0.33–2.28)) during the follow-up. No significant differences were found in pain induced limitations between CPAP- and oral appliance therapy. Pre-therapeutically, one patient in the CPAP group was classified as suffering from pain induced limitation. However, this patient was also familiar with orofacial pain complaints. These complaints did not increase during the follow-up period and were no reason for the patient to cease CPAP-therapy. In the oral appliance group, also one patient was pre-therapeutically classified as suffering from pain induced limitation. During the follow-up period these complaints disappeared.

Regarding mandibular function impairment, no significant differences between oral appliance therapy and CPAP therapy were observed at the different time-points (β=0.56, 95% CI (-1.77-2.88)). For the oral appliance group, no association was found between the mean mandibular protrusion during the follow-up (β=-0.23 (-2.83–13.90)), therapy use (β=0.96 (-0.29–2.21)), possible switching of therapy (β=0.02 (-1.24-1.28)) and the MFIQ scores at different time-points.

Regarding the function impairment score, at baseline, all patients could be classified as 'low' impairment (FIRS 0 or 1). After two months of treatment (T2), 1 patient using an oral appliance and 1 patient using CPAP was classified with 'moderate' impairment. At the one-year follow-up (T15), the same patient in the oral appliance group remained being classified with 'moderate' impairment. In the CPAP group, 2 patients suffered from 'severe' impairment at the one year follow-up (T15). At the last follow-up visit (T27), 1 patient in the oral appliance group still suffered from 'moderate' impairment, and one of the patients who was 'severely' impaired in the CPAP group was now classified as being 'moderately' impaired. The other patient remained 'severely' impaired.

Discussion

To our knowledge this is the first study in which the occurrence of different TMDs as a result of long-term oral appliance therapy at different time-points has been evaluated in a controlled study concerning patients from the full OSAS spectrum. This study shows that in the initial period after initiating oral appliance or CPAP therapy, the occurrence of (particularly pain-related) TMDs increases, being substantially higher (24%) in the oral appliance group than in the CPAP group (6%). Furthermore, we found that oral appliance therapy results in significantly more pain during a two-year follow-up compared with CPAP therapy. This pain did not induce limitations of the temporomandibular complex, neither in the oral appliance- nor in the CPAP group. No differences were found in mandibular function impairment during the two-year follow-up between oral appliance- and CPAP therapy. No relationship could be found between the mean mandibular protrusion, and the frequency of wearing the appliance during follow-up with the occurrence of pain and function impairment of the temporomandibular complex.

The occurrence of TMDs as a result of long-term oral appliance therapy has been described previously by Martinez-Gomis and co-workers (23). They found that the occurrence of TMDs at different time-points was not affected by long-term oral appliance therapy in OSAS patients. In the present study, the occurrence of pain-related TMDs after 2-3 months of using an oral appliance (T2) was considerably higher as compared to baseline, in contrast to the CPAP group. This could be the result of the strain in the muscles of the temporomandibular complex or the capsular ligament of the temporomandibular joint (TMJ) when protruding the mandible during sleep. The condyle of the mandible is positioned out of its natural resting position into a more forward and downward position, resulting in possible strain of the retro-discal tissue. Another possible explanation is the increase in occlusal vertical dimension while wearing an oral appliance. Le Belle and co-workers showed that after applying artificial occlusal interferences, the occurrence of temporomandibular pain symptoms increased, but decreased after a few days (32). Therefore, the authors suggest that patients can adapt to a new vertical occlusal situation. In a study by Giannasi and co-workers, the intensity of TMDs symptoms decreased significantly after oral appliance therapy (25). Particularly the occurrence of jaw fatigue decreased during the follow-up period. These authors hypothesized that protruding the mandible results in less compression of

the TMJ and related structures. Unfortunately, a matched control group was absent in this study, so it remains unclear to what extent oral appliance therapy contributes to these phenomena. Furthermore, in the latter study, the Helkimo Anamnestic Dysfunction Index was used. This index has been developed for epidemiological purposes and not, like the RDC/TMD Axis I used in this study, for clinical purposes. The Helkimo Anamnestic Dysfunction Index furthermore classifies patients into three "dysfunction" groups rather than clinical diagnoses. In the present study we did not find a clinical relevant change during the follow-up of different TMDs occurrences in the oral appliance group compared with the CPAP group. After the initial increase of different (pain-related) TMDs and combinations thereof in the oral appliance group, the occurrence decreased to values similar to baseline during the follow-up. This finding suggests that the temporomandibular complex has adaptive capacities to the unnatural protrusive position during sleep while wearing an oral appliance. After 2-3 months of therapy, all pain-related TMDs had decreased in the oral appliance group in the remaining period of the follow-up. From that perspective it appears that an oral appliance could have a therapeutic effect in patients with TMDs. It has been described that treatment with an anterior repositioning splint reduces reciprocal clicking of the TMJ (33). Because the oral appliance used in this study also positions the mandible in a forward position, it could be hypothesized that patients with a TMD experience a favourable effect. However, scientific evidence for this possible phenomenon is weak (34). Furthermore the number of patients in our study may be too low to draw conclusions with respect to this possible effect. Moreover, it has been described that in some patients with disc displacement without reduction, symptoms did resolve spontaneously over time without treatment (35).

The results of this study show that patients with OSAS, treated with an oral appliance, have a higher risk of developing pain in the temporomandibular complex (OR 2.33) as compared to CPAP therapy. However, this pain is most pronounced in the initial period of oral appliance treatment and tends to decrease afterwards. These findings correspond with the results of other studies (10, 20, 22, 25). It has been described that OSAS patients with TMDs could benefit from mandibular exercises during oral appliance therapy (36). This might suggest that support therapy could reduce TMD-related pain, probably resulting in higher compliance rates in the initial phase of oral appliance therapy. However, in a research setting, the risk of nonadherence in patients suffering from oromandibular pain may be little as patients are frequently monitored. Conversely, in a regular clinical setting, nonadherence due to TMD problems might hamper the outcome of the results.

No significant differences were found in mandibular function impairment between the oral appliance- and CPAP group. Since a dose dependency of oral appliance therapy on the AHI has previously been described (13, 37), it is conceivable that in severe OSAS patients, oral appliance therapy might result in more mandibular function impairment. However, we did not find an association between the mandibular protrusion during the follow-up, and the MFIQ scores at different time-points. This finding corresponds with the results of another study (13) that also did not show a difference in adverse effects on the stomatognatic system between patients with 50% and 75% mandibular protrusion during a 6 month follow-up. We also did not find an as-

sociation between therapy use or switch of therapy and MFIQ scores or pain intensity. This could partially be explained by the fact that there were only minor differences in therapy use, making it more difficult to discriminate between these patients. Moreover, only few patients switched to the alternative therapy during the follow-up period.

In the present study, patients with active TMDs (e.g. osteoarthritis) and restrictions in mouth opening (< 25 mm) or advancement of the mandible (< 5 mm) were excluded. This resulted in a total occurrence of single TMD or combinations of TMDs in 29% of our total study group assessed with the RDC/TMD. In another study (24) the occurrence of TMDs at baseline was 52%. These findings suggest that standardized criteria for TMDs diagnosis, such as the RDC/TMD, should be part of a standard examination in order to discriminate between active and inactive TMDs, prior to oral appliance therapy, as it should be considered a life-long treatment unless alternative therapies can bring help.

After randomisation, a difference in TMDs between both groups at baseline (23% for CPAP and 35% for oral appliance) was observed and more women (16%) were allocated to the oral appliance group compared to the CPAP group (6%). As it is known that TMDs occur more frequently in women than men (38), this could be a possible confounding factor. However, we believe that the total amount of women in our study was too low to distort our results. Nevertheless, we did not study these possible effects in detail.

Considering the fact that OSAS is a disorder with serious cardiovascular consequences, it should be treated as effective as possible. Discontinuation of oral appliance therapy because of the development of TMDs should only be considered in patients who are able to tolerate or accept another effective treatment modality for their OSAS.

In conclusion, our results show that the occurrence of (pain-related) TMDs increases in the initial period of oral appliance therapy but tends to return to baseline values during a 2-year follow-up. In OSAS patients, oral appliance therapy results in more pain of the temporomandibular complex compared to CPAP therapy, but does not cause pain-induced limitations in these patients. Mandibular function was not impaired in OSAS patients using an oral appliance or CPAP therapy for two years. These findings suggest that the possible development of TMDs or temporary pain of the temporomandibular complex is not a contra-indication for oral appliance therapy in OSAS patients.

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CHAPTER 5

Maxillomandibular advancement surgery as alternative to continuous positive airway pressure in morbidly severe obstructive sleep apnoea; a case report

Submitted

This chapter is an edited version of:
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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, characterized by disrupted snoring and repetitive upper airway obstructions (1). Patients suffering from OSAS have a predisposition to repetitive upper airway collapse during sleep, which can be the result of anatomical abnormalities or fat depositions surrounding the upper airway. The latter is most pronounced in overweighed patients. OSAS is associated with an increased risk of cardiovascular events and associated morbidity and mortality. The condition also results in excessive daytime sleepiness, fatigue and neurocognitive deficits (2). Severity of OSAS is usually expressed by the apnoea-hypopnoea index (AHI), i.e., the mean number of apnoeas and hypopnoeas per hour sleep. By convention, OSAS is classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI >30) (3).

The standard treatment, continuous positive airway pressure (CPAP), relieves upper airway obstructions and improves quality of life (4). Because of the cumbersome nature of CPAP, patients may abandon or adhere poorly to this treatment. Oral appliance therapy is an effective alternative, and is especially effective in mild-to-moderate OSAS cases (5). Most oral-appliances used in a clinical setting are mandibular advancement devices (MAD's), which keep the mandible and its attached musculature in a protruded position. Successful oral appliance therapy has been suggested as a predictor for successful maxillomandibular advancement (MMA) surgery in OSAS patients (6). MMA surgery has gained increasing popularity in this field since this procedure is associated with an enlargement of the entire velo-oro-hypopharyngeal airway. This specific surgical procedure may be indicated for treatment of severe OSAS patients who cannot tolerate or are unwilling to adhere to CPAP therapy. MMA surgery may also be contemplated in patients in whom oral appliances, which are more often appropriate in mild and moderate OSAS patients, have been considered undesirable (7). The aims of this case report were:

1. to describe the value of MMA surgery after (partially) successful oral-appliance therapy in a patient with morbidly severe OSAS and CPAP intolerance.
2. to gain insight in the three-dimensional upper changes associated with MMA surgery.

Case report

A 32-year-old female was referred by the Department of Home Mechanical Ventilation to the Department of Oral and Maxillofacial Surgery of the University Medical Center Groningen because of respiratory problems and CPAP intolerance. She suffered from morbidly severe OSAS (AHI=139) and was morbidly obese (body mass index (BMI) = 40). Her lowest oxyhemoglobin saturation during sleep was 73%. Daily functioning was severely compromised because of excessive daytime sleepiness (EDS). Furthermore, she was diagnosed with left ventricular hypertrophy (LHV) and was treated for essential hypertension. She tried CPAP therapy (pressure 9 cmH2O) for a month but this resulted in discomfort in the maxillary sinuses and distress during the night. During physical and radiological examination a mandibular retrognathia and pronounced cervi-

comental fat deposition was observed (Fig. 1A). Intra-oral examination revealed a bulky tongue, which obscured visualization of the soft palate and uvula (modified Mallampati class IV). Because of inadequate oral hygiene there was some marginal gingivitis. Further intra-oral examination revealed a healthy dentition without active periodontal disease. To improve oral hygiene, the patient was referred to an oral hygienist for plaque removal and oral hygiene instructions. The lateral cephalogram showed a narrow posterior airway space at the level of the base of the tongue (Fig. 2A).

After full examination of the temporomandibular complex it was decided to make an oral appliance. The oral appliance (Thornton Adjustable Positioner, Airway Management Inc., Dallas, TX, USA) consisted of two separate parts, fixing the patient's mandible in a protruded and downward position. The mandibular protrusion could be adjusted with a propulsion screw, which was incorporated anteriorly in the oral appliance. When initiating oral-appliance therapy, the mandible was set at approximately 60% of the patient's maximum protrusion. After having adapted to this position during a two-week period, the patient was allowed to further adjust the oral appliance until OSAS symptoms abated or adjustments became uncomfortable. At the final follow-up review, 4 weeks later, the patient reported that she slept and felt much better. She also reported a substantial decrease in her daytime sleepiness. To quantify the result of oral-appliance therapy, a polysomnographic study with oral appliance in place was conducted 6 weeks after initiating therapy. The AHI decreased from 139 to 40, which was considered a major reduction. Lowest oxyhemoglobin saturation during sleep improved from 73% to 76%. The patient was very positive about the treatment effects and was treated with an oral appliance for about 4 months. However, her severe OSAS persisted despite oral appliance therapy. Furthermore, she indicated to prefer a more "permanent" solution for her condition. Since she also complained about a lack of chin projection in her profile, she opted for MMA surgery, combined with a genioplasty and cervicomental liposuction. Presurgical orthodontics was regarded cumbersome in combination with the oral appliance. Moreover, the temporary use of CPAP during orthodontic treatment was, due to earlier negative experiences, not a serious option in this specific case. Therefore it was decided to perform orthognathic surgery without orthodontic treatment. Her class 1 occlusion would therefore be preserved following surgery.

Based on soft- and hard tissue cephalometric analyses, using the true vertical line (TVL), a surgical plan was made. MMA surgery was planned in such a manner that an optimal airway enlargement was combined with an aesthetically pleasing surgical outcome. For this reason a counter clockwise rotation of the maxillomandibular complex was planned. As a result a large advancement of the mandible is accompanied with a posterior downgraft of the maxilla and thereby relatively less advancement of the upper jaw. This results in less paranasal puffiness which may be expected when a straight forward advancement of the maxillomandibular complex of 10 mm would be planned. A modified genioplasty, comparable to Plenier and Delaire (8), with advancement of the suprahyoid and genioglossal musculature was also planned. This procedure consists of a trapezoid-shaped advancement osteotomy of the chin to establish an additional forward stretching of the tongue and hyoid musculature (9). With this procedure the upper part of the

Figure 1. Thirty-three year old female with morbidly severe obstructive sleep apnoea syndrome. Photograph of the (A) preoperative profile and (B) postoperative profile.

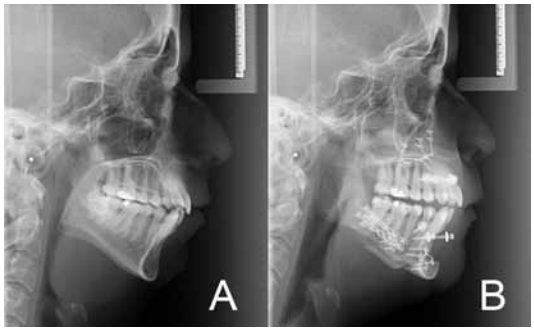

Figure 2. Cephalogram of the (A) preoperative situation and (B) postoperative situation.

labial cortex of the advanced chin can be removed and used as bonegraft at the zygomatic buttresses at the Le Fort 1 level.

After preoperative placement of orthodontic brackets MMA surgery was performed under general anaesthesia. A bilateral sagittal split osteotomy (BSSO) of the mandible was performed with counter clockwise rotation and advancement of 10 mm at B point and fixed with two miniplates on both sides. After this, a standard le Fort 1 osteotomy was performed with posterior downgraft of 3 mm at the level of the first molars and advancement of 8,5 mm at the incisal edge of the central incisors leaving the existing occlusion practically unchanged. The maxilla was fixed with four miniplates. The modified genioplasty, as described previously, was performed with an advancement of 6 mm. After this a cervicomental liposuction was performed using a small stab incision just behind the submental fold in the facial midline. At the end of the surgery, the zygomatic buttresses were grafted with mandibular bonegrafts from the chin. The bony defect between the proximal and distal segments of the mandible that resulted from the BSSO was grafted with a mix of bone particles and hydroxyapatite. The wounds were closed primarily and miniscrews were placed in the anterior region of mandible and maxilla in order to put the patient on postoperative skeletal elastics in combination with dental elastics on the brackets. The patient was extubated at the end of the surgery and stayed overnight in the recovery room to guarantee

continuous (oxyhemoglobin) monitoring. There were no surgical or medical complications in the direct post-operative period.

Four months after surgery another polysomnographic study was performed. There was almost a complete resolution of the patients' OSAS with a postoperative AHI of 6, which consisted only of hypopnoeas and no apnoeas. The lowest oxyhemoglobin saturation during sleep was 86%. The patient reported to feel 'reborn' after surgery. She experienced her sleep as undisturbed and reported a resolution of her excessive daytime sleepiness. Furthermore, she was very pleased with her new facial appearance (Fig. 1B). The tracings (Fig. 5) of the preoperative (Fig. 2A) and postoperative (Fig. 2B) cephalograms illustrate the profound skeletal and soft-tissue changes as a result of surgery.

3-D Image acquisition and analysis

Maxillofacial noncontrast conebeam-CT (CBCT) scans were taken pre- and postoperative (i-CAT, Imaging Sciences International, Hatfield, USA). At each acquisition the patient was seated in an upright position, asked to hold their breath at end-expiration with the dentition in maximal occlusion and the lips in relaxed contact position. The CBCT scans were imported in Simplant Crystal software (Materialize Dental, Leuven, Belgium). In the axial slides the superior boundary of the 3D airway figure was set at the posterior nasal spine and the inferior boundary was set at the base of the epiglottis. The minimum retropalatal and retroglossal cross-sectional area (CSA) of the upper airway was calculated pre-, and postoperatively. After surgery, a substantial increase was found in anterior-posterior and lateral airway dimensions of the upper airway at the retropalatal level (increase minimal cross-sectional area from 114 mm^2 to 276 mm^2) and retroglossal level (increase minimal cross-sectional area from 109 mm^2 to 188 mm^2) (Fig. 3 and 4).

Discussion

This case report shows the effectiveness of MMA surgery after positive results of oral-appliance therapy in a patient with severe OSAS and CPAP intolerance. This finding confirms the results of the study performed by Hoekema and co-workers (6), in which patients with a substantial reduction in the baseline AHI with oral appliance therapy appeared to be good candidates for MMA surgery. However, that study was retrospective in design and included only four patients undergoing MMA surgery. It would therefore be of great value to perform a prospective study to investigate the predictive value of oral appliance therapy outcome for MMA surgery in a larger group of patients.

The patient described in this case report had a baseline AHI of 139, which may be considered morbidly severe OSAS. Oral appliance therapy resulted in a major decrease of the AHI to 40 but the remaining OSAS was still severe. It is known that oral appliance efficacy declines with increasing OSAS severity (10). This is explained by the fact that patients with severe OSAS are generally more obese with oral appliance therapy generally being less effective in these patients

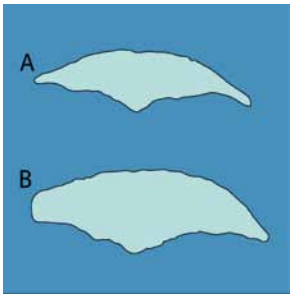

Figure 3. Minimal cross-sectional area of the upper airway at retroglossal level (A) preoperative (B) postoperative.

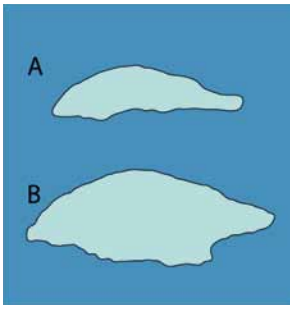

Figure 4. Minimal cross-sectional area of the upper airway at retropalatal level (A) preoperative (B) postoperative.

(10). Furthermore, oral appliance therapy only protrudes the mandible while the maxillary position remains unchanged. In MMA surgery, the mandible as well as the maxilla are positioned anteriorly, which could explain the superior efficacy of MMA surgery over oral appliance therapy in our patient. The additional maxillary advancement pulls the velum and velopharyngeal muscles forward, most possibly creating more space at the velopharyngeal level of the upper airway. In a systematic review it has been reported that the degree of maxillary advancement was indicative for surgical success (11). Furthermore, in a cephalometric analysis it was found that the increase of the posterior airway space at velopharyngeal level, associated with wearing an oral appliance, was the best predictor for a decrease in the AHI (12). These findings suggest the importance of maxillary advancement in addition to mandibular advancement when treating OSAS patients by means of MMA surgery.

Fairburn and co-workers reported varying results regarding efficacy of MMA surgery in severe OSAS patients (13). In a few of their patients, respiratory parameters deteriorated after MMA surgery. One of their explanations for this finding is the negative effect of scarring as a result of previous upper airway surgery (e.g. uvulopalatopharyngoplasty). Our patient did not undergo any type of upper airway surgery before the present procedure, which could have had a favourable effect in this specific case. Younger age, lower preoperative BMI and AHI are considered predictors of successful MMA surgery in OSAS patients (7). However, our patient was morbidly obese and had an extremely high AHI but was still treated very effectively following this procedure. This finding may be explained by the fact that our patient was additionally treated with a genioplasty and cervicomental liposuction. These procedures may have added to the positive effect of MMA

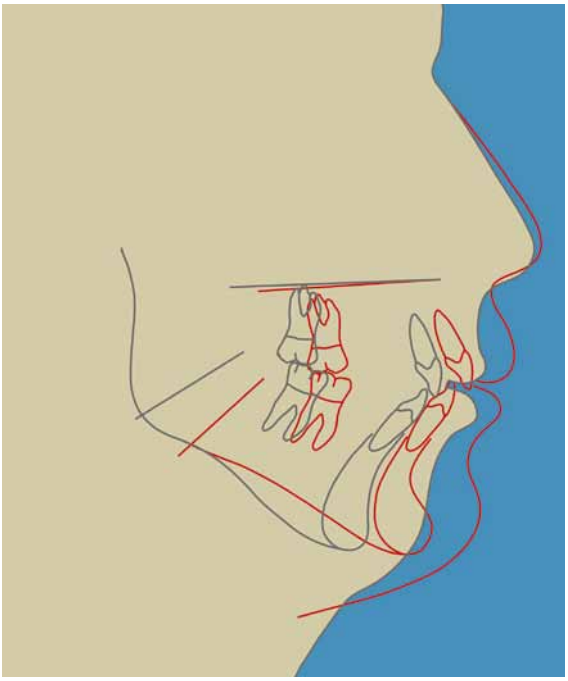

Figure 5. Superimposed (S-N) preoperative (grey line) and postoperative tracings (red line) of lateral cephalograms.

surgery on upper airway patency.

As a result of the enlargement of the lateral and anterior-posterior dimensions of the upper airway following MMA surgery, an increase in the cross sectional area of the upper airway was found at retropalatal and retroglossal levels. This finding is consistent with results, published in previous studies (13, 14). Studies evaluating upper airway changes as a result of wearing an oral appliance also show an increase of the cross sectional area of the upper airway at different levels (15, 16). Choi and co-workers report a decrease of the cross-sectional area (range 36.5%-75.5%) of the upper airway during midazolam-induced sleep in the supine position. In most studies including this case report, patients were evaluated during upper airway assessment in an upright position while being awake. However, in this case report the pre- and postoperative CB-CT studies were performed, using exactly the same protocol. We therefore believe that the changes we found in the upper airway cross sectional areas after MMA surgery are of clinical importance.

In a recent conducted controlled study it was found that there was no significant difference in success rate between MMA surgery and CPAP in severe OSAS patients (17). These findings may indicate and confirm that, in the future, MMA surgery can take a prominent place in treating severe OSAS patients who do not tolerate CPAP or in patients who are unwilling to use CPAP.

In conclusion this case report shows that MMA surgery combined with a modified genioplasty and cervicomental liposuction can be very effective in treating morbidly severe OSAS in a morbidly obese patient. MMA surgery was in fact the only effective treatment for this patient's life-threat-

ening disorder. Furthermore, this case substantiates the observation that effective treatment with an oral appliance (mandibular advancement device) can be considered a good predictor for successful MMA surgery in OSAS management. Lateral and anterior-posterior upper airway dimensions increase at the retropalatal and retroglossal level as a result of MMA surgery combined with a genioplasty and submental liposuction. To clarify which patients would benefit from MMA therapy, a multidisciplinary evaluation is recommended.

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CHAPTER 6

General discussion & conclusions

Oral appliance therapy is currently considered a successful treatment for patients with mild and moderate obstructive sleep apnoea syndrome (OSAS) and has emerged as an increasingly popular alternative to continuous positive airway pressure therapy (CPAP). The advantages of oral appliance therapy over CPAP include its high acceptance, reversibility, ease of use, the lack of noise, no power source required, and portability.

Several clinical trials have confirmed the short-term success of oral appliance therapy in OSAS patients (1-8). As oral appliance therapy should be considered a life-long treatment, it is important to know whether it is a successful treatment on the long-term and to gain insight into the specific side-effects, related to long-term use of an oral appliance. However, controlled trials, addressing the long-term success of oral appliance therapy and investigating the development of side-effects associated with long-term oral appliance use in mild-to-severe OSAS, are scarce.

The aims of this thesis were to evaluate:

1. morphological changes of the upper airway in patients wearing an oral appliance,
the objective and subjective outcomes of long-term (2-years) oral appliance- and CPAP therapy in mild-to-severe OSAS patients,
2. possible side-effects on the craniofacial morphology, the dentition and the temporomandibular complex associated with long-term (2-years) use of an oral appliance.
3. The present chapter discusses the main findings of this thesis. Furthermore, suggestions for future research in the field of sleep medicine are provided.

Upper airway morphology

It is assumed that the working mechanism of an oral appliance is based on the advancement of the mandible and its attached soft tissue structures and musculature, possibly resulting in an increased tone with increased anteroposterior and lateral dimensions of the upper airway (9, 10). Because of this working mechanism one would expect an increase in upper airway patency while wearing an oral appliance. There are several ways of studying the upper airway, each of which has its (dis)advantages. We studied the changes in upper airway morphology as a result of wearing an oral appliance by cephalometry and found an increase in the anterior-posterior dimension of the upper airway at various levels (**Chapter 2**). It could be hypothesized that increasing the vertical dimension in occlusion, associated with wearing an oral appliance, might compromise the anterior-posterior upper airway dimensions by rotation of the mandible. However, our results did not show a decrease in anterior-posterior upper airway dimensions. The amount of mandibular protrusion probably overrules this possible negative effect of increasing the vertical dimension.

Advantages of cephalometry are its accessibility, low costs and relatively low radiation exposure for the patient. However, this two-dimensional image only provides information about the anterior-posterior dimension of the upper airway and yields no information regarding lateral dimensions. Furthermore, cephalometric imaging is usually performed in an upright position, which does not resemble the patient's natural sleeping position. Nowadays, three-dimensional computed tomography (CT) imaging techniques, like cone-beam CT, have emerged progressively as a

diagnostic tool in dentistry and oral- and maxillofacial surgery. Cone-beam CT has been used for diagnosis, treatment planning, and outcome assessment in patients with OSAS (11, 12). In OSAS patients, it has been demonstrated that there is an increase in lateral, in addition to anterior-posterior, dimensions of the upper airway while wearing an oral appliance (13). In our case-report (**Chapter 5**) we used cone-beam CT analysis to study changes in upper airway dimensions as a result of maxillomandibular advancement (MMA) surgery in a patient with severe OSAS. In this study we also found an increase in anterior-posterior and lateral dimensions of the upper airway. However, cone-beam CT analysis is more expensive and less available in dental clinics. Though, the upper airway should preferably be studied in three dimensions. By doing so, one could gain more insight in the complex pathophysiology and working mechanisms of different treatment modalities for OSAS. After CT imaging, additional computational fluid dynamics can gain insight in the airflow and resistance of the upper airway in OSAS patients (14). Unfortunately, even this complex and expensive imaging technique, cannot completely reveal the complex and dynamic pathophysiology of OSAS. In clinical practice, a cephalogram with an anterior bite registration can be compared with a baseline cephalogram to gain insight in the changes in the anterior-posterior upper airway dimensions. The baseline cephalogram can be used to study the amount of overbite and overjet, the maxilla-mandibular relationship and the vertical level of the hyoid, as these parameters might provide prognostic information about treatment success with an oral appliance (15).

Treatment outcome

There is increasing evidence that an oral appliance is a successful treatment alternative to CPAP in mild and moderate OSAS patients. Several comparative studies have been published, in which the effects of oral appliance therapy have been compared with CPAP (1-8, 16-18). All but three studies (2, 3, 18) used a crossover design. Two studies used a randomized controlled parallel design with only an oral appliance- and CPAP group (2, 3). In the study of Aarab and co-workers (3) it was found that treatment with an oral appliance as well as with CPAP significantly lowered the apnoea-hypopnoea index (AHI). However, no significant difference in changes in the AHI between both treatments was found. Hoekema and co-workers (2) concluded that oral appliance therapy was not inferior to CPAP with regard to the percentage of successful treatments in mild-to-severe OSAS. It was also concluded that oral appliance therapy was specifically successful in patients with mild and moderate disease.

From our two-year follow-up study of this specific patient cohort (**Chapter 3**) we can conclude that, regarding the percentage of successful treatments, oral appliance therapy was not inferior to CPAP in treating mild-to-severe OSAS. Nevertheless, regarding polysomnographic variables, CPAP showed a significantly lower AHI and higher oxygen saturation levels compared with oral appliance therapy. Even with respect to the two-year follow-up, our results endorse the latest practice parameters of the American Academy of Sleep (19), in which oral appliance therapy "is recommended in mild and moderate patients who prefer an oral appliance, do not respond to

CPAP, are unsuitable for CPAP, or who fail to adhere to CPAP." However, notwithstanding the fact that CPAP was more effective (74%) in treating severe OSAS, we found that in 50% of the patients with severe OSAS (AHI>30), treatment with an oral appliance appeared to remain successful after a two-year treatment period. This latter finding corroborates the results of the study of Mehta and co-workers (20), who concluded that oral appliance therapy can be considered as a first-line treatment for certain severe OSAS patients. Further research is required to predefine which specific severe OSAS patients may benefit from oral appliance therapy.

Another aspect that requires consideration is the criterion for treatment success. In the literature many different definitions of 'treatment success' have been used, mostly solely based on lowering the AHI below a predefined threshold. In comparative studies 'success' is defined as AHI <10 (5-7, 17, 21, 22), as AHI <10 with a reduction in the AHI >50% (23), as AHI <15 (24), or as a reduction in the AHI >50% (25). According to the criteria of the American Academy of Sleep Medicine, OSAS is defined as AHI >5 in combination with OSAS-related symptoms (26). Therefore, we believe that 'treatment success' should be defined as an AHI <5. Furthermore, because of the regression-to-the-mean phenomenon, one could get the impression that despite much greater reductions in the AHI in severe patients, treatment is less successful as it is harder to reach an AHI <5 for a patient with a baseline AHI of 80 than for a patient with a baseline AHI of 8. Moreover, OSAS-related symptoms are an important factor in the patients' daily life and should be incorporated in the definition of 'treatment success'. Because of the above mentioned reasons we adapted the criterion also used in other controlled trials (20, 27, 28) in which success was defined as an AHI <5 or an AHI <20 with at least a 50% reduction of the baseline AHI in a patient free of OSAS-related symptoms. Because of the various different criteria of treatment success it is hard to compare outcomes between different studies. Therefore, uniformly accepted success criteria should be used in order to compare results from different studies.

In our study more patients dropped out or switched oral appliance therapy (47%) compared to CPAP therapy (33%) during the two-years of follow-up. In a recent review (29) of nine conducted RCTs comparing oral appliance therapy with CPAP, it was described that patients preferred oral appliance therapy over CPAP in 6 studies (4, 6-8, 16, 17) and CPAP over oral appliance therapy in 2 studies (1, 5). In one study, patient preference data were not described as that study was not a cross-over but a parallel design (2). Therefore, patients were not able to express their preferred treatment. However, patients' preference is only one of the factors that determine dropout rates. In our two-year follow-up, 'success of treatment' also was an important variable that determined the dropout rates for both treatments. Two patients in the oral appliance group and 6 patients in the CPAP group dropped out or switched because of adherence problems during the follow-up period. Furthermore, 14 patients in the oral appliance group and 6 patients in the CPAP group dropped out or switched because of a nonsuccessful treatment. The difference in dropout rates in our study could be explained by the fact that we did not exclude severe OSAS patients. Most studies comparing oral appliance therapy with CPAP only included mild and moderate OSAS patients. After two months of treatment, 7 patients switched from oral appliance therapy to CPAP therapy. These patients had a higher AHI, were older and more obese compared to the patients

that switched from CPAP to oral appliance therapy. As a lower baseline AHI (15), younger age, lower BMI and smaller neck circumference (20, 30) are associated with better treatment outcome, it is likely that those patients are treated nonsuccessfully with an oral appliance and were randomized for the unfavourable treatment group in retrospect. A second explanation could be the tendency of oral appliance therapy to decrease in efficacy in the long term (31). In our study more patients dropped out in the oral appliance group because of a nonsuccessful treatment response compared to CPAP during the two-year follow-up. A plausible explanation for this deterioration in treatment response might be a stretching or loosening effect of the muscles and soft tissue of the upper airway as a result of long-term overnight mandibular advancement. Further research is needed to study the upper airway soft tissue responses (e.g. muscle tone and length) as a result of long-term oral appliance use and to evaluate which specific patients are prone to a relapse of treatment success in the long term.

Despite the above-mentioned considerations, our findings suggest that, for the long-term, oral appliance therapy may be considered as first-line treatment alternative for mild and moderate OSAS patients. Furthermore, oral appliance therapy seems to be successful in a substantial part of patients with severe OSAS but should only be considered in those patients unwilling or unable to tolerate CPAP.

Side-effects

In this thesis, three studies (**Chapter 4.1, 4.2 and 4.3**) address side-effects associated with long-term use of an oral appliance. All these three studies are unique compared to most other published studies concerning side effects associated with oral appliance therapy, as there always was a control group (CPAP). Therefore, we corrected for changes that might have occurred with increasing age. Little is known about long-term side-effects of oral appliance use in mild-to-severe OSAS patients. In contrast, short-term side-effects of oral appliance therapy have been described extensively and include tooth pain, occlusal changes in the morning, dry mouth or excessive salivation, gum irritation, temporomandibular joint pain, temporomandibular joint sounds and myofascial pain (6, 21, 32-36).

As oral appliance therapy can be considered a life-long treatment, it is important to know what consequences can be expected from long-term oral appliance use, as pre-therapeutically, patients need to be thoroughly and realistically informed about the possible side-effects of therapy. Our results demonstrate that long-term use of oral appliance causes small but significant dental changes. Our most prominent finding was a decrease of overjet and overbite measured with cephalometry (**Chapter 4.1**) and an association between the mean mandibular protrusion during follow-up and the decrease in overbite. Both findings were corroborated in the study on dental side-effects, assessed on plaster cast study models (**Chapter 4.2**). Furthermore, we found a retroclination of the upper incisors and a proclination of the lower incisors as a result of oral appliance therapy. Changes in overbite and overjet, retroclination of the upper incisors and a proclination of the lower incisors have also been described in previous studies (32, 35, 37, 38). Conversely,

Ringqvist and co-workers did not find significant changes in overbite, overjet, and inclination of the upper or lower incisors after two years of oral appliance use (39). First, oral appliance design might have contributed to these differences, as the appliance used by Ringqvist and co-workers did not cover the frontal parts of both tooth arches, probably causing less palatally directed forces on the upper incisors and less labially directed forces on the lower incisors. Another explanation could be the degree of mandibular protrusion during oral appliance therapy of only 50% of the maximum mandibular protrusion in the Ringqvist study. In our study, protrusive positions of the mandible over 75% of the patient's maximum protrusion were applied in some patients. As we found an association between the amount of long-term mandibular protrusion and the decrease in overbite, it is conceivable that dental side-effects are more pronounced in our patients than observed in the study by Ringqvist and co-workers.

In our study-model analysis (**Chapter 4.2**) we found a tendency towards a mesiocclusion after two years of oral appliance therapy compared to CPAP therapy. In the oral appliance group we also found a tendency towards the development of a (bi)lateral crossbite in the (pre)molar region and a decrease in occlusal contact points in the (pre)molar region. Some of these side-effects can be classified as 'favourable' or 'unfavourable' as suggested by Almeida and co-workers (37). We mostly found 'favourable' dental changes in patients with a baseline class II occlusion (e.g. correction to class I or decrease in overjet) and mostly found 'unfavourable' changes in patients with a baseline class I occlusion (e.g. change to class III occlusion or development of a (bi)lateral open bite). From that perspective, one should be alert when treating patients with a class I occlusion with an oral appliance. Especially in these patients, but also in general, possible side-effects of oral appliance therapy should be discussed with the patient pre-therapeutically and informed consent should be obtained before starting treatment.

As already mentioned, oral appliance design might influence the development of (dental) side-effects with long-term oral appliance use. However, no comparative studies are available, studying long-term side-effects comparing different types of oral appliances. In our study we did not assess the possible relationship between the patient's periodontal status and the extent of dental side-effects. One can hypothesize that a decreased number of healthy teeth or a decrease in periodontal supporting tissue could speed up or worsen the development of dental side-effects as the forces, associated with oral appliance therapy, are transmitted to a reduced periodontal surface. In future studies it should be considered for future research to take the patient's periodontal status into account before and during oral appliance therapy and to relate this factor to the degree of dental-changes that occur.

Regarding side-effects on the temporomandibular complex (**Chapter 4.3**) we concluded that oral appliance therapy is associated with increased pain compared to CPAP in the initial period. This pain is usually of mild and transient nature. The development of temporomandibular disorders (TMDs) and/or function impairment appears to be limited with long-term oral appliance use. TMDs were assessed using the Research Diagnostic Criteria (RDC) for TMD (Axis I). For assessing TMDs, no gold standard was available at the time the present study was started. The RDC/TMD have been developed to classify and diagnose TMDs according to reproducible protocols and

could, therefore, be a reliable instrument for research purposes. However, there are some shortcomings to the RDC/TMD (Axis I). First, some outcomes are no diagnoses but rather describe a symptom or symptoms (e.g. myalgia, arthralgia). Secondly, it was found that the specificity of the RDC/TMD tests in patients with chronic dental pain was much lower (45%) than that in pain-free subjects (71%) (40). Third, the RDC/TMD do not contain a diagnostic taxonomy for TMD pain that is based on pathologic mechanisms and aetiology. However, despite these shortcomings, we believe that the RDC/TMD constitute a reproducible instrument for classifying and diagnosing TMDs for research purposes, which makes our outcomes comparable to other studies

In the three studies regarding side-effects of long-term oral appliance therapy, we showed that there are significant (dental) side-effects in a substantial number of our patients. Although the majority of these patients do not experience any inconvenience or impairment, serious problems can arise if side-effects are progressive over the years. Therefore, it could be advised to undergo alternative treatment like maxillomandibular advancement (MMA) surgery in an earlier phase, in patients treated successfully with an oral appliance. MMA surgery should only be applied in carefully selected patients as aesthetics are almost always changed after surgery. It can provide definitive treatment and, thus, eliminate problems regarding compliance with other treatments. In our case report (**Chapter 5**) we showed that MMA surgery can play a role in morbidly obese patients suffering from severe OSAS who do not tolerate CPAP therapy. Our patient showed a tremendous improvement in polysomnographic outcomes but also a substantial subjective improvement. There is however, still a lack of high-level scientific evidence. Furthermore, there is no universal treatment algorithm that includes polysomnographic parameters, health, performance and quality-of-life variables (41).

Concluding remarks and future perspectives

The aims of this thesis were to evaluate the changes in upper airway morphology, to assess the objective and subjective treatment outcome of long-term oral appliance therapy, and to assess side-effects associated with long-term use of an oral appliance.

Conclusions and related future perspectives

The following conclusions can be drawn, giving rise to several related future perspectives.

Wearing an oral appliance results in increased anterior-posterior dimensions of the upper airway at the level of the second vertebra, the base of the tongue and the uvular tip. Future research should focus on 3-D imaging of the upper airway as lateral dimensional changes appear to play an important role in the working mechanism of oral appliance therapy. This should be studied with the patient in the supine position, preferably during sleep, as this resembles the clinical situation.

On the long-term, no significant difference was found regarding the percentage of successful treatments between oral appliance therapy and CPAP in treating mild-to-severe OSAS. However, regarding polysomnographic variables, CPAP is more effective in lowering the AHI and shows

higher oxygen saturation levels compared to oral appliance therapy.

Future research should focus on the role of oral appliance therapy in severe, but also mild and moderate OSAS and on specific characteristics that are predictive for treatment success of oral appliance therapy in these patients. This selection of OSAS patients, suitable for oral appliance therapy might prevent high drop-out rates during long-term treatment. In order to compare compliance between both CPAP and oral appliance therapy, another aspect for future research is the option to covertly measure compliance to oral appliance therapy.

Most side-effects associated with long-term oral appliance therapy involve changes in the patient's dental occlusion, of which a decrease in the overjet and overbite are the most striking manifestations. Side-effects of long-term oral appliance therapy on the temporomandibular complex include myalgia and arthralgia but are mostly present in the initial phase of treatment therapy and are of mild and transient nature. Nevertheless, oral appliance therapy should be considered as a life-long treatment, and there is a risk of (sometimes serious) side-effects to occur. Therefore, it is of the utmost importance that patients treated with an oral appliance, need a thorough follow-up by a dentist or dental-specialist, who is experienced in the field of dental sleep medicine.

Future research should focus on differences in oral appliance design in relation to the development of side-effects as there are many different designs, each which their own (dis)advantages and different mechanisms in force distribution. Furthermore, the relationship between periodontal status and the development of side-effects is still unknown and needs further investigation.

Other future perspectives

As our case report illustrates, maxillomandibular advancement (MMA) surgery can be a very effective and definitive surgical solution for severe OSAS patients. MMA surgery is now a surgical intervention which is, according to multiple treatment guidelines, at the end of the treatment spectrum for OSAS patients. It could be suggested to use MMA surgery as a permanent solution for OSAS patients in an earlier stage, for example, after a certain period of successful treatment with an oral appliance. It remains to be established whether successful oral appliance is a good predictor for successful treatment with MMA surgery. To clarify which patients would benefit from MMA surgery, a multidisciplinary evaluation remains recommended.

OSAS is a known risk factor for developing sustained periods of hypertension, cardiovascular diseases, or death. Though, little is known about the effects of oral appliance therapy on cardiovascular variables. Future randomized trials should focus on cardiovascular outcome parameters (e.g. blood pressure, advanced glycation end products (AGE) measurements and intima-media thickness (IMT) measurements of the arteries). These outcomes may affect general medical practice and medical costs can be studied from a societal perspective, including direct costs inside and outside the health care sector, as well as indirect costs.

In some patients with severe OSAS, CPAP needs to be adjusted to inconvenient high pressures, possibly resulting in compliance problems. Oral appliances can be used as alternative treatment although therapy is not always effective enough. A combination of CPAP and oral appliance therapy may provide another option for CPAP-intolerant patients with incomplete response to oral appliance therapy (42).

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CHAPTER 7.1

Summary

Summary

Sleep disorders commonly occur in the general population and may give rise to serious repercussions on general health, social life and daily functioning. The obstructive sleep apnoea syndrome (OSAS) is a sleep-related breathing disorder, which is characterized by intense snoring and recurrent obstructions of the upper airway during sleep. These upper airway obstructions can either be complete (apnoeas) or partial (hypopnoeas). The severity of OSAS is usually expressed as the apnoea-hypopnoea index (AHI), defined as the average number of apnoeas and hypopnoeas per hour sleep and is assessed through a sleep registration (e.g., polysomnography). Based on the outcome of this polysomnographic study, OSAS is classified as mild (AHI 5-15), moderate (AHI 15-30) or severe (AHI> 30).

When treating OSAS, clinicians may consider various non-invasive, surgical or pharmacological treatment modalities. When conservative treatment is not applicable or effective, continuous positive airway pressure (CPAP) used to be the preferred intervention in OSAS patients. Although very effective, the obtrusive nature of the flow generator and (oro)nasal mask, may cause patients to cease or adhere poorly to CPAP therapy. Over the past decades, intra-orally worn dental devices, commonly known as oral appliances, have gained increasing popularity as treatment alternative to CPAP therapy. The most common type of oral appliance is the mandibular repositioning appliance (MRA). An MRA aims at relieving upper airway obstructions by positioning the mandible and its attached soft tissues structures in a forward and downward position during sleep.

Nowadays, oral appliance therapy has been demonstrated to be an effective alternative in treating OSAS. There is however a lack of controlled studies comparing the efficacy of oral appliance therapy and CPAP therapy in the long term in OSAS patients representing the entire spectrum of the disorder. Furthermore, controlled studies regarding side effects, associated with long-term oral appliance use are scarce.

Therefore, the general aims of the studies described in this thesis were to evaluate the long-term efficacy and side-effects of oral appliance- and CPAP therapy.

In **chapter 2** a study is described assessing the change in upper airway morphology associated with an oral appliance in situ in patients suffering from OSAS and to relate these changes to treatment response. Lateral cephalograms were taken at baseline and after 2-3 months of treatment. Baseline and follow-up cephalograms were traced twice and cephalometric variables were compared. The predictive value of changes in upper airway morphology for the treatment response was evaluated in univariate and multivariate regression analyses. Our study shows that wearing an oral appliance results in an increased posterior airway space at the level of the second vertebra, the uvular tip and the base of the tongue. The increase of the posterior airway space at the level of the second vertebra and the uvular tip were the best predictors for relative improvement of the apnoea-hypopnoea index. However, the predictive value for treatment response of these cephalometric upper airway changes should be interpreted with caution.

In **chapter 3** we describe the objective and subjective treatment outcome of oral appliance- and CPAP therapy in a two-year follow-up. In 103 patients, objective and subjective parameters were assessed after one year and two years of treatment. Treatment was considered "successful" when the AHI was <5 or showed 'substantial reduction', defined as reduction in the index of at least 50% from the baseline value to a value of < 20 in a patient without OSAS symptoms while using therapy. Regarding the percentage of successful treatments, no significant difference was found between oral appliance therapy and CPAP in treating mild-to-severe OSAS in a two-year follow-up. CPAP was still successful in 67% of the patients and oral appliance therapy in 53% of the patients (p=0.14) after two years of treatment. Both therapies showed substantial improvements in polysomnographic and neurobehavioral outcomes. However, CPAP was more effective in lowering the AHI and showed higher oxygen saturation levels compared to oral appliance therapy (p<0.05).

In **chapter 4.1** a study is described in which the craniofacial morphology associated with long-term use of an oral appliance compared with CPAP in patients with OSAS was assessed. Fifty-one patients were randomized to oral appliance therapy and fifty-two patients tot CPAP therapy. At baseline and after follow-up (2.3 ± 0.2 years) (mean ± standard deviation), a lateral cephalogram of all patients was made in maximum intercuspation to determine relevant cephalometric variables. Both baseline and follow-up cephalograms were traced digitally whereupon cephalometric variables were compared. Compared with CPAP, long- term use of an oral appliance resulted in small but significant (dental) changes. Overbite and overjet decreased, 1.0 (±1.5) mm and 1.7 (±1.6) mm, respectively. Furthermore we found a retroclination (-2.0 ± 2.8 degrees) of the upper incisors and a proclination (3.7 ± 5.4 degrees) of the lower incisors. Moreover, the lower- and total anterior facial height increased significantly, 0.8 (± 1.5) mm and 0.9 (± 1.4) mm, respectively. No changes in skeletal variables were found. Linear regression analysis revealed that the decrease in overbite was associated with the mean mandibular protrusion during follow-up.

Chapter 4.2 focuses on possible dental side-effects op long-term oral appliance therapy compared with CPAP. As part of a previously described study (**chapter 3**), 51 patients were randomized to oral appliance therapy and 52 patients to CPAP therapy. At baseline and after a two-year follow-up, dental plaster study models in full occlusion were obtained which were thereupon analyzed with respect to relevant variables. Long-term use of an oral appliance resulted in small but significant dental changes compared with CPAP. In the oral appliance group, overbite and overjet decreased, 1.2 (±1.1) mm and 1.5 (±1.5) mm, respectively. Furthermore, we found a significantly larger anterior-posterior change in the occlusion (-1.3 ± 1.5 mm) in the oral appliance group compared to the CPAP group (-0.1 ± 0.6 mm). Moreover, both groups showed a significant decrease in number of occlusal contact points in the (pre)molar region. Linear regression analysis revealed that the decrease in overbite was associated with the mean mandibular protrusion during follow-up.

Long-term oral appliance use is associated with dental side-effects. Therefore, patients treated with an oral appliance, need dental check-ups by a dentist or dental-specialist at regular intervals.

While using an oral appliance during sleep, the mandible is positioned in an unnatural ventral position. On the longterm this could give rise to side-effects on the temporomandibular complex. In **chapter 4.3** variations in the occurrence of temporomandibular disorders (TMDs) and the risk of developing pain and function impairment of the temporomandibular was assessed. In addition, the relationship between the mean mandibular protrusion, and the frequency of wearing the appliance during follow-up with the occurrence of pain and function impairment of the temporomandibular complex was assessed. Fifty-one patients were randomized to oral appliance therapy and fifty-two patients to CPAP therapy as part of the in **chapter 3** described study. TMDs (diagnosed according to the Axis I Research Diagnostic Criteria for TMD), pain intensity and disability, and mandibular function impairment were recorded at baseline, after 2 months, 1 year and 2 years of therapy. Only in the initial period of treatment the occurrence of pain-related TMDs was considerably higher (24%) in the oral appliance group compared to CPAP (6%). Oral appliance therapy furthermore resulted in more temporomandibular pain compared to CPAP (Odds ratio 2.33, 95% Confidence Interval (1.22 – 4.43)). However, there were no limitations in mandibular function in both groups during the (entire) follow-up period. Although generally not serious and of transient nature, oral appliance therapy results in more pain related TMDs in the initial period of use compared with CPAP therapy. Because of the transient nature, this pain is not a reason to contra-indicate an oral appliance in OSAS patients. Moreover, TMDs and the risk of developing pain and function impairment of the temporomandibular complex appear limited with long-term oral appliance use.

Successful oral appliance therapy has been suggested as a predictor for successful maxillomandibular advancement (MMA) surgery in OSAS patients. MMA surgery has gained increasing popularity in this field since this procedure is associated with an enlargement of the entire velo-oro-hypopharyngeal airway. This specific surgical procedure may be indicated for treatment of severe OSAS patients who cannot tolerate or are unwilling to adhere to CPAP therapy. In **chapter 5** a case is described of a 32-year-old morbidly obese (BMI=40) female with morbidly severe OSAS (AHI=139) and micrognathia of the mandible. As she was considered CPAP intolerant, an oral appliance was made which made her AHI drop to 40. Afterwards, she underwent MMA surgery combined with a modified genioplasty and cervicomental liposuction. Post-surgically, there was almost a complete resolution of the patients' OSAS with a postoperative AHI of 6, which consisted only of hypopnoeas and no apnoeas. The lowest oxyhemoglobin saturation during sleep was 86%. The patient reported to feel 'reborn' after surgery. She experienced her sleep as undisturbed and reported a resolution of her excessive daytime sleepiness.

In **chapter 6** the main research outcomes of this thesis are discussed in broader context and general conclusions are drawn. Furthermore, this chapter discusses and suggests aspects that may be considered for future research in oral appliance therapy for OSAS. From the research described in this thesis it can be concluded that, in the long-term, oral appliance therapy can be

considered as a first-line treatment, next to CPAP in mild and moderate OSAS patients. However, CPAP remains most effective in patients with severe OSAS. Furthermore, long-term oral appliance therapy is associated with various side-effects of which dental side-effects or the most prominent. Therefore, patients treated with an oral appliance should be regularly checked by a dentist or dental-specialist experienced in the field of dental sleep medicine.

CHAPTER 7.2

Samenvatting

Samenvatting

Slaapstoornissen komen regelmatig voor onder de algemene bevolking en kunnen ernstige gevolgen hebben voor de gezondheid, het sociale leven en het dagelijks functioneren. Het obstructief slaapapneu syndroom (OSAS) is een slaapgerelateerde ademhalingsstoornis, die wordt gekenmerkt door intensief snurken en herhaaldelijke obstructies van de bovenste luchtweg tijdens de slaap. De obstructies van de bovenste luchtweg kunnen volledig (apneu) of gedeeltelijk (hypopneu) voorkomen. De ernst van de aandoening wordt meestal uitgedrukt in de "apneu-hypopneu index" (AHI), gedefinieerd als het gemiddelde aantal apneus en hypopneus per uur slaap en wordt beoordeeld middels een slaapregistratie (bijv. polysomnografie). Op basis van de uitkomst van dit polysomnografisch onderzoek, wordt OSAS geclassificeerd als mild (AHI 5-15), matig (AHI 15-30) of ernstig (AHI> 30).

Bij de behandeling van OSAS, staat de clinicus verschillende conservatieve, chirurgische of farmacologische behandelmodaliteiten ter beschikking. Als conservatief behandelen niet toepasbaar of ineffectief bleek bij OSAS patiënten, ging de voorkeur uit naar de behandeling middels continue positieve luchtwegdruk (Eng.; continuous positive airway pressure [CPAP]). Ondanks de hoge effectiviteit, kunnen patiënten door het belastende karakter van deze behandeling stoppen met de therapie of kan de therapietrouw te wensen overlaten. In de afgelopen decennia zijn intraoraal gedragen tandheelkundige apparaten gegroeid in populariteit als behandelalternatief voor CPAP. De meest voorkomende vorm van intraorale apparaten is het mandibulaire repositie apparaat (MRA). Behandeling met een MRA is gericht op het verminderen van de bovenste luchtweg obstructies door het verplaatsen van de onderkaak en de daaraan gehechte weke delen naar ventraal en caudaal tijdens de slaap.

Tegenwoordig is behandeling met intraorale apparaten een effectief alternatief gebleken in de behandeling van OSAS. Er is echter een gebrek aan gecontroleerde studies naar de effectiviteit van intraorale apparaten en CPAP-therapie op de lange termijn bij OSAS patiënten die het gehele spectrum van de aandoening vertegenwoordigen. Bovendien zijn gecontroleerde studies schaars welke betrekking hebben op neveneffecten, geassocieerd met langdurig gebruik van intraorale apparaten.

De algemene doelstellingen van dit proefschrift zijn het evalueren van de lange termijn effectiviteit en neveneffecten van intraorale apparaten en CPAP-therapie.

In **hoofdstuk 2** wordt een studie beschreven waarin veranderingen van de bovenste luchtwegmorfologie, geassocieerd met een intraoraal apparaat in situ, werden vastgesteld in patiënten met OSAS. Tevens werd gekeken of deze veranderingen gerelateerd waren aan de therapierespons. Laterale schedelfoto's werden vervaardigd bij aanvang van de therapie (zonder intraoraal apparaat) en 2-3 maanden nadien (met intraoraal apparaat in situ). De laterale schedelfoto's van baseline en follow-up werden twee keer getraceerd en cephalometrische variabelen werden vergeleken. De voorspellende waarde van veranderingen in de bovenste luchtweg morfologie voor therapierespons werd geëvalueerd in univariate en multivariate regressie analyses. Uit deze studie

bleek dat het dragen van een intraoraal apparaat resulteert in een verruiming van de bovenste luchtweg op het niveau van de tweede cervicale wervel, de tip van het uvula en de tongbasis. De verruiming van de bovenste luchtweg op het niveau van de tweede cervicale wervel en de tip van het uvula waren de beste voorspellers voor een relatieve verbetering van de AHI. Echter, de voorspellende waarde voor therapierespons van deze cephalometrische veranderingen van de bovenste luchtweg dient met voorzichtigheid te worden geïnterpreteerd.

In **hoofdstuk 3** beschrijven we de objectieve en subjectieve respons op therapie met een intraoraal apparaat en CPAP in een twee jaar durende follow-up bij een cohort van 103 OSAS patiënten welke eerder in een gerandomiseerde gecontroleerde studie hebben geparticipeerd. Objectieve en subjectieve parameters werden geëvalueerd na één en twee jaar behandeling. De behandeling werd als "succesvol" gezien als de AHI <5 was of als er sprake was van een "aanzienlijke reductie" van de AHI, gedefinieerd als een reductie van de AHI van ten minste 50% t.o.v. de baseline waarde tot een waarde van <20 in een patiënt zonder OSAS symptomen onder therapie. Met betrekking tot het percentage succesvolle behandelingen, werd geen significant verschil gevonden tussen behandeling met een intraoraal apparaat en CPAP bij patiënten met een mild tot ernstig OSAS gedurende een follow-up van twee jaar. CPAP was nog steeds succesvol in 67% van de patiënten en behandeling met een intraoraal apparaat in 53% van de patiënten ($p = 0.14$) na twee jaar behandelen. Beide therapieën lieten aanzienlijke verbeteringen in polysomnografische en neurofysiologische variabelen zien. Desalniettemin was CPAP effectiever in het reduceren van de AHI en werden hogere zuurstofsaturatie waarden gezien vergeleken met de behandeling met een intraoraal apparaat ($p <0.05$).

In **hoofdstuk 4.1** worden eventuele neveneffecten op de craniofaciale morfologie beschreven, welke veroorzaakt kunnen worden door langdurig gebruik van een intraoraal apparaat vergeleken met CPAP bij OSAS patiënten. Eenenvijftig patiënten werden in het kader van een eerder uitgevoerde gecontroleerde klinische studie (**hoofdstuk 3**) gerandomiseerd voor behandeling met een intraoraal apparaat en tweeënvijftig patiënten voor CPAP. Bij aanvang en na de follow-up (2.3 ± 0.2 jaar) (gemiddelde ± standaard deviatie), werd een laterale schedelfoto vervaardigd bij alle patiënten tijdens maximale occlusie om relevante cephalometrische variabelen te bepalen. Zowel de laterale schedelfoto's van baseline en follow-up werden digitaal getraced waarna cephalometrische variabelen werden vergeleken. In vergelijking met CPAP, resulteerde langdurig gebruik van een intraoraal apparaat in kleine, maar significante (dentale) veranderingen. De overbeet en overjet namen gemiddeld af met respectievelijk 1.0 (± 1.5) mm en 1.7 (± 1.6) mm. Verder vonden we een retroclinatie (-2.0 ± 2.8 graden) van de centrale bovenste snijtanden en een proclinatie (3.7 ± 5.4 graden) van de centrale onderste snijtanden. Bovendien is de onderste en de totale anterieure gezichtshoogte significant toegenomen, 0.8 (± 1.5) mm en 0.9 (± 1.4) mm, respectievelijk. Er werden geen veranderingen in skeletale variabelen gevonden. Lineaire regressie analyse liet zien dat een afname van de overbeet werd geassocieerd met de gemiddelde mandibulaire protrusie tijdens de follow-up.

Hoofdstuk 4.2 richt zich op mogelijke tandheelkundige nevenwerkingen van intraorale apparaten in vergelijking met CPAP op lange termijn. Als onderdeel van een eerder beschreven studie (**hoofdstuk 3**), werden 51 patiënten gerandomiseerd voor behandeling met een intraoraal apparaat en 52 patiënten voor CPAP. Bij aanvang en na een twee jaar therapie, werden studiemodellen van het gebit in maximale occlusie verkregen en geanalyseerd. Langdurig gebruik van intraorale apparaten resulteerde in kleine, maar significante dentale veranderingen vergeleken met CPAP. In de groep die behandeld werd met een intraoraal apparaat nam de overbeet en overjet gemiddeld af met 1.2 (± 1.1) mm en 1.5 (± 1.5) mm, respectievelijk. Verder vonden we een grotere gemiddelde anterieure-posterieure verandering in de occlusie (-1.3 ± 1.5 mm) in de groep die behandeld werd met een intraoraal apparaat vergeleken met de CPAP groep (-0.1 ± 0.6 mm). Bovendien vertoonden beide groepen een significante daling in het aantal occlusale contactpunten in het (pre)molaar gebied. Uit lineaire regressie analyse bleek dat afname van de overbeet geassocieerd was met de gemiddelde mandibulaire protrusie tijdens de follow-up periode.

Geconcludeerd kan worden dat langdurig gebruik van een intraoraal apparaat geassocieerd wordt met dentale neveneffecten. Daarom moeten patiënten die behandeld worden met een intraoraal apparaat, regelmatig voor follow-up worden gezien door een tandarts(specialist) die ervaring heeft op het gebied van de tandheelkundige slaapgeneeskunde.

Tijdens het gebruik van een intraoraal apparaat tijdens de slaap, wordt de onderkaak in een onnatuurlijk ventrale positie gehouden. Op de lange termijn kan dit aanleiding geven tot neveneffecten op het temporomandibulaire complex. In **hoofdstuk 4.3** worden variaties in het optreden van temporomandibulaire stoornissen en het risico op het ontwikkelen van pijn en functiebeperking van het temporomandibulaire complex beschreven bij patiënten die behandeld worden met een intraoraal apparaat of CPAP. Bovendien is gekeken naar de relatie tussen de gemiddelde mandibulaire protrusie, de draagfrequentie van het apparaat tijdens de follow-up en het optreden van pijn en functiebeperking van het temporomandibulaire complex. Eenenvijftig patiënten werden gerandomiseerd voor behandeling met een intraoraal apparaat en tweeënvijftig patiënten voor CPAP als onderdeel van de in **hoofdstuk 3** beschreven studie. Temporomandibulaire stoornissen (gediagnosticeerd volgens Axis I: Research Diagnostic Criteria for Temporomandibular Disorders), intensiteit van de pijn, beperking door de pijn en mandibulaire functiebeperking werden bepaald bij aanvang van de therapie, na 2 maanden, na 1 jaar en na 2 jaar therapie. Vooral in de beginperiode van de behandeling waren pijn-gerelateerde temporomandibulaire stoornissen aanzienlijk frequenter aanwezig (24%) in de groep die behandeld werd met een intraoraal apparaat vergeleken met de CPAP groep (6%). Bovendien leidde behandeling met een intraoraal apparaat tot meer temporomandibulaire pijn vergeleken met CPAP. Er werd echter geen mandibulaire functiebeperking waargenomen in beide groepen gedurende de (gehele) follow-up periode. Behandeling met een intraoraal apparaat leidt tot meer pijn-gerelateerde temporomandibulaire stoornissen in de eerste periode van gebruik in vergelijking met CPAP-therapie. Deze zijn echter mild en van voorbijgaande aard. Daarom is deze pijn geen reden om een intraoraal apparaat te contra-indiceren in OSAS patiënten. Bovendien lijken temporomandibulaire stoornissen en het

risico op het ontwikkelen van pijn en functiebeperkingen van het temporomandibulaire complex beperkt bij langdurig gebruik van een intraoraal apparaat.

Er wordt gesuggereerd dat succesvolle behandeling met een intraoraal apparaat van voorspellende waarde kan zijn voor succesvolle behandeling middels een maxillomandibulaire osteotomie bij OSAS patiënten. Een maxillomandibulaire osteotomie betreft een chirurgische verplaatsing van de boven- en onderkaak naar voren. De procedure wordt gezien als de meest effectieve chirurgische behandeling van het OSAS. De maxillomandibulaire osteotomie wordt mondiaal in toenemende mate toegepast bij OSAS patiënten sinds bekend is dat deze procedure gepaard gaat met een toename van het lumen van de gehele velo-oro-hypofaryngeale luchtweg. Deze specifieke chirurgische procedure kan worden geïndiceerd bij de behandeling van patiënten met een ernstig OSAS die CPAP niet kunnen verdragen of niet therapietrouw zijn aan CPAP. In **hoofdstuk 5** wordt een casus beschreven van een 32-jarige vrouw met morbide obesitas (BMI = 40), een zeer ernstig OSAS (AHI = 139) en een onderontwikkeling van de onderkaak. Omdat CPAP therapie niet effectief was en dit gepaard ging met teveel neveneffecten, werd een intraoraal apparaat vervaardigd waarna een AHI van 40 werd bereikt. Hier opvolgend onderging zij een maxillomandibulaire osteotomie, gecombineerd met een gemodificeerde genioplasty en cervicomentale liposuctie. Postoperatief was er nog slechts sprake van een zeer mild OSAS met een postoperatieve AHI van 6, die enkel bestond uit hypopneus. De laagste zuurstofsaturatiewaarde tijdens de slaap was 86%. Patiënte voelde zich als 'herboren' na de operatie. Ze ervaart haar slaap als ongestoord en verder is er geen sprake meer overmatige slaperigheid overdag.

Deze casus laat zien dat een maxillomandibulaire osteotomie ook effectief kan zijn bij een patiënt met een zeer ernstig OSAS als CPAP therapie niet geaccepteerd wordt.

In **hoofdstuk 6** worden de belangrijkste onderzoeksresultaten van dit proefschrift in een breder perspectief geplaatst en worden algemene conclusies getrokken. Verder worden suggesties gegeven voor toekomstig onderzoek naar behandeling met intraorale apparaten. Uit het onderzoek beschreven in dit proefschrift kan worden geconcludeerd dat, ook op lange termijn, behandeling met een intraoraal apparaat als behandeling van eerste keus kan worden beschouwd bij patiënten met mild en matig OSAS. CPAP blijft echter het meest effectief bij patiënten met ernstig OSAS. Verder wordt langdurige behandeling met een intraoraal apparaat geassocieerd met diverse neveneffecten, waarvan de dentale neveneffecten het meest prominent zijn. Daarom moeten patiënten die worden behandeld met een intraoraal apparaat regelmatig worden gecontroleerd door een tandarts(specialist) die ervaring heeft op het gebied van de tandheelkundige slaapgeneeskunde.

Appendix

Appendix to chapter 3

Recruitment of patients

The University Medical Center Groningen has a catchment area that includes most of the north-eastern part of The Netherlands. Patients suspected to have sleep apnoea are referred to this medical center by general practitioners from the region and physicians from departments of pulmonary medicine, neurology, and ear, nose, & throat surgery in several regional hospitals in order to possibly participate in a previously conducted randomized controlled trial (RCT) (10). We used the recommendations of the American Academy of Sleep Medicine to diagnose obstructive sleep apnoea (1) and are defined as:

1 or 2, plus criterion 3 of the following:

1. A clear decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep. Baseline is defined as the mean amplitude of stable breathing and oxygenation in the two minutes preceding onset of the event (in individuals who have a stable breathing pattern during sleep) or the mean amplitude of the three largest breaths in the two minutes preceding onset of the event (in individuals without a stable breathing pattern).
2. A clear amplitude reduction of a validated measure of breathing during sleep that does not reach the above criterion but is associated with either an oxygen desaturation of >3% or an arousal.
3. The event lasts 10 seconds or longer.

Each patient diagnosed as having obstructive sleep apnoea consulted our Department of Home Mechanical Ventilation for treatment.

Selection of patients and informed consent

To screen for any underlying disease, all eligible patients underwent a comprehensive physical evaluation, spirometry, thoracic radiography, electrocardiography, and blood tests.

General criteria for inclusion in the study were:

- age >20 years old.
- polysomnography showing an apnoea-hypopnoea index ≥ 5; i.e., the mean number of apnoeas and hypopnoeas per hour of sleep in combination with:
  - Excessive daytime sleepiness that is not better explained by other factors or
  - Two or more of the following that are not better explained by other factors:
    - choking or gasping during sleep,
    - recurrent awakenings from sleep,
    - unfreshed sleep,
    - daytime fatigue,
    - impaired concentration.

Medical and psychological criteria for exclusion from the study were:

- previous treatment of obstructive sleep apnoea (continuous positive airway pressure (CPAP), oral appliance therapy, or uvulopalatopharyngoplasty).

- morphological airway abnormalities requiring treatment (a compromised nasal passage, enlarged tonsils or adenoids, upper-airway or pulmonary neoplasm, or upper-airway soft tissue or craniofacial abnormality).
- endocrine dysfunction (hypothyroidism, acromegaly, or pituitary adenoma).
- a reported or documented history of severe cardiac or pulmonary disease (daytime respiratory insufficiency, severe chronic obstructive pulmonary disease (Tiffeneau-index <40%) (2), heart failure, coronary disease, or severe cardiac arrhythmias).
- moderate or severe periodic limb movement disorder (periodic limb movement index >25).
- a psychological condition precluding informed consent (mental retardation or psychiatric disorder; e.g., depression or schizophrenia).

Dental criteria for exclusion from the study were:

- extensive periodontal disease or tooth decay.
- active temporomandibular joint disease (including severe bruxism).
- restrictions in mouth opening (<25 mm) or advancement of the mandible (<5 mm).
- partial or complete edentulism (<8 teeth in upper or lower jaw).

Patients who qualified for inclusion were informed about the study and their questions were answered by the pulmologist and dentist who evaluated the patients. Each patient was given a brochure with details about the study and had 1 week to decide whether or not they wanted to participate. Patients who decided to participate signed and returned an informed consent form.

Randomization procedure

The clinical epidemiologist (B.S.) for the study made computer-generated randomization sequences, balancing for disease severity. The randomization sequences were used for selecting random permuted blocks with lengths of 2, 4, and 6 (3). The clinicians supervising oral appliance- and CPAP therapy were not informed about how the randomization was performed. The randomization sequences were concealed and administered by the secretarial office of the Department of Oral and Maxillofacial Surgery. After each patient's serial number and diagnosis of disease severity was provided, the treatment was disclosed. Each serial number could be provided only once. It was not possible to blind patients or clinicians to treatment assignment.

Interventions, conservative measures, and adjustments

Oral appliance therapy was initiated in the Department of Oral and Maxillofacial Surgery and was supervised by two experienced dentists (M.D, A.H.). CPAP therapy was initiated in the Department of Home Mechanical Ventilation. Oral appliance therapy was initiated within a 4-week period and CPAP therapy within a 2-week period after a patient was enrolled in the study. Before treatment was initiated, all patients were instructed to adopt conservative measures; specifically, to avoid using depressants (e.g., alcohol, sleep medication) and to have at least 7 to 8 hours of sleep each night. When indicated, patients were encouraged to give up smoking and loose weight.

The oral appliance used in this study consisted of two separate parts (4). The upper part was

supported by the dentition of the maxilla and the lower part by the dentition of the mandible. By turning a propulsion screw incorporated anteriorly in the appliance, the patient could adjust the amount of mandibular advancement in 0.2-mm increments. The maximum advancement of the mandible was determined with a George-Gauge™ (H Orthodontics, Michigan City, IN, USA) before oral appliance therapy began. Initially, the mandible was set at 50% of the patient's maximum advancement. After patients became accustomed to the oral appliance during a 2-week period, they returned for a check-up visit. They were instructed to adjust the oral appliance over the following 6 weeks, until the second polysomnographic study was performed—advancing the mandible by turning the propulsion screw each night with 1 or 2 clockwise turns (i.e., 0.2–0.4 mm) until symptoms abated (i.e., snoring, apnoeas, hypopnoeas, or excessive sleepiness). If the second polysomnographic assessment indicated an apnoea-hypopnoea index ≥5, the oral appliance was adjusted, if possible, in an attempt to improve effectiveness. The oral appliance was adjusted to obtain the maximum advancement of the mandible with which the patient was comfortable. A third polysomnographic study was performed 4 weeks after that adjustment was made.

CPAP titration was performed during an afternoon nap (5). All patients using CPAP received detailed instructions about this procedure and use of CPAP from a skilled nursing consultant. Patients were fitted with a comfortable CPAP mask before titration. After CPAP titration, all patients received a similar CPAP device (Breas® PV10, Mölnlycke, Sweden). Patients were permitted to become accustomed to CPAP during a 2-week period, after which they returned for a check-up visit. After another 6 weeks of treatment, a second polysomnographic study was performed. If polysomnography indicated an apnoea-hypopnoea index ≥5, we adjusted the CPAP, if possible, with a rise in pressure by 1 or 2 cm H_2O, depending on the residual apnoea-hypopnoea index with CPAP. A third polysomnographic study was performed 4 weeks after that adjustment was made (T2). Adjustments of CPAP therapy were continued until the apnoea-hypopnoea index was <5 or until adjustments of CPAP became uncomfortable for the patient.

Patients for whom oral appliance- or CPAP therapy was successful continued the treatment. Patients for whom treatment was not effective were offered the alternative CPAP or oral appliance therapy. After one year (T15) and two years (T27) of treatment another polysomnographic study was performed.

Polysomnography

Surface electroencephalography, submental electromyography, and left and right electrooculography were used to stage sleep by using standardized criteria (6). A pulsoximeter (Oximeter Flex Sensor – 8000J-3, Medcare, Reykjavik, Iceland) was used to record oxyhemoglobin saturation. Electrocardiography was used to monitor cardiac function. Oronasal airflow was recorded with a pressure cannula. Respiratory effort was monitored with thoracic and abdominal strain gauges. An anterior tibial electromyogram was recorded to screen for periodic limb movements. Each polysomnographic study started at 11 AM and ended at 9 AM the next morning. Polysomnographic outcomes were assessed during the night while the patient was asleep. Outcomes

included total sleep time, sleep efficiency, apnoea-hypopnoea index, minimum oxyhemoglobin saturation, the percentage of non-rapid eye-movement sleep during stages 1 & 2 and 3 & 4, and the percentage of rapid eye-movement sleep. Baseline polysomnographic outcomes were those obtained at the time of diagnosis.

Neurobehavioral examinations

Patients completed the Epworth sleepiness scale to assess their propensity to fall asleep in eight different situations (7). Patients completed the functional outcomes of sleep questionnaire to assess the impact of excessive sleepiness on a number of activities of everyday living (8). This questionnaire consists of 30 different questions that yield a score for five different subscales and a total score. Patients completed the medical outcomes study 36-item short-form health survey to assess their perception of their health status (9). This questionnaire consists of 11 questions that yield a score for eight different dimensions and one item regarding changes in the patient's health.

Patients' usage of their therapy was evaluated by asking patients how many nights each week and how many hours each night they used their treatment. Whereas CPAP usage can be monitored covertly with a mechanism built into the device, oral appliance usage cannot be assessed covertly in any reliable way. To eliminate bias, we ensured that treatment usage was assessed in the same manner by basing the assessments on self-reports in both groups. Some patients did not use treatment during the entire week; for example, on weekends when they did not anticipate a strenuous day. Patients were considered non-adherent to therapy only if they voluntarily discontinued use of the therapy due to poor tolerance or any other reason.

Statistical analysis

Calculation of the sample size was performed with the PASS 2000 software package (NCSS, Kaysville, UT). Statistical analyses were performed by using the Statistical Package for the Social Sciences (version 16.0, SPSS Inc., Chicago, IL, USA). The clinical epidemiologist (B.S.) who collected and analyzed all the data did not have any contact with the patients. Power analysis was done for a previously conducted two-month RCT (10) of which this study is the two-year follow-up. For that RCT, a minimum of 46 patients would be required in each treatment group when a one-sided significance level of 5%, a power of 90%, and an assumed proportion of treatment effectiveness of 90% was applied.

Table E1. Characteristics of patients that switched to the alternative therapy during the follow-up.

Variable	Oral appliance after CPAP* (n = 4)	CPAP after oral appliance* (n = 7)
Male/female ratio	4/0	5/2
Apnoea-hypopnoea index (no/hour)	33 ± 15	60 ± 42
Age (years)	43 ± 11	51 ± 12
Body-mass index (kg/m^2)	30 ± 2	39 ± 6
Neck circumference (cm)	44 ± 1	46 ± 5

* Plus-minus values are means ± standard deviations.
Abbreviations: CPAP = continuous positive airway pressure.

Table E2. Characteristics of the patients included in the final analysis.

Variable	Oral appliance* (n = 29)	CPAP* (n = 37)
Male/female ratio	23/6	35/2
Apnoea-hypopnoea index (no/hour)	36 ± 22	44 ± 28
Age (years)	50 ± 9	51 ± 10
Body-mass index (kg/m^2)	31 ± 6	34 ± 5
Neck circumference (cm)	43 ± 3	45 ± 4

* Plus-minus values are means ± standard deviations.
Abbreviations: CPAP = continuous positive airway pressure.

Table E3. Proportions of successful treatments with an oral appliance or with continuous positive airway pressure according to the criterion AHI<5.

Successful treatment	Two-month follow-up (T2)*		One-year follow-up (T15)*		Two-year follow-up (T27)*	
	Oral appliance	CPAP	Oral appliance	CPAP	Oral appliance	CPAP
Total population	29 / 51 (56.9%)	40 / 52 (76.9%)	24 / 51 (47.1%)	34 / 52 (65.4%)	20/ 51 (39.2%)	33 / 52 (63.5%)†
Non-severe sleep apnoea	21 / 25 (84.0%)	20 / 25 (80.0%)	14 / 25 (56.0%)	15 / 25 (60.0%)	12 / 25 (48.0%)	13 / 25 (52.0%)
Severe sleep apnoea	8 / 26 (30.8%)	20 / 27 (74.1%)	10/ 26 (38.5%)	19 / 27 (70.4%)†	8 / 26 (30.8%)	20 / 27 (74.1%)†

*Values are the number of successful treatments divided by the total number of patients. Values in parenthesis are the percentages of patients with an AHI<5.
† Significant difference ($p<0.05$) (chi-square test) in the proportions of successful treatments between oral appliance- and CPAP therapy.
Abbreviations: CPAP = continuous positive airway pressure.

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Appendix

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Curriculum Vitae

Michiel Doff graduated in Mechanical Engineering (2002) and Dentistry (2007) in Groningen. During his dental training he started as a (D)MD/PhD-student within the Junior Scientific Masterclass (www.jsmgroningen.nl). His research, as described in this thesis, was conducted at the department of oral and maxillofacial surgery of the University Medical Center Groningen (Head: Prof. dr. L.G.M. de Bont) in close collaboration with the department of Home Mechanical Ventilation and the department of Clinical Neurophysiology. After his graduation he worked as a general dentist in several clinics. From 2009 to 2011 he worked at Scheperziekenhuis Emmen, were he was trained in oral surgery and dental implantology. During that period he also worked at the Center of Dental Implantology (CTI) Haaksbergen. Michiel started his oral and maxillofacial residency in 2011 at the University Medical Center Groningen (UMCG). He was one of the initiators and is vice-chairman of the Dutch Society of Dental Sleep Medicine (NVTS). Michiel lives in Groningen and has a son (Simon).